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Interleukin-4 (IL-4) Inhibitor Prior Authorization with Quantity Limit Program Summary

FDA APPROVED INDICATIONS AND DOSAGE[1]

Agent(s)	Indication(s)	Dosage
Dupixent® (dupilumab) Injection for subcutaneous use	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.	Adults: Initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week 6-17 years of age: • 15 kg to <30 kg: Initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every 4 weeks • 30 kg to <60 kg: Initial dose of 400 mg (two 200 mg injections), followed by 200 mg given every other week • ≥60 kg: Initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week
	Add-on maintenance treatment in patients with moderate-to-severe asthma aged 6 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma. Limitation of Use: Not indicated for the relief of acute bronchospasm or status asthmaticus	12 years of age and older: Initial dose of 400 mg (two 200 mg injections), followed by 200 mg given every other week **OR** Initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week For patients 12 years of age and older with oral corticosteroid-dependent asthma, or with co-morbid moderate-to-severe atopic dermatitis, start with an initial dose of 600 mg followed by 300 mg given every other week 6-11 years of age: • 15 to <30 kg: 100 mg every other week **OR** 300 mg every 4 weeks • ≥30 kg: 200 mg every other week No initial loading dose is recommended in patients 6-11 years of age, unless there is also co-morbid moderate-to-severe atopic dermatitis. In that scenario, dosing follows the

		"atopic dermatitis" pediatric dosing recommendation.
	Add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP)	300 mg given every other week

CLINICAL RATIONALE

Atopic Dermatitis

Atopic dermatitis (AD), also known as atopic eczema, is a chronic, pruritic inflammatory dermatosis affecting up to 25% of children and 1-5% of adults. AD follows a relapsing course and is associated with elevated serum immunoglobulin (IgE) levels and a personal or family history of type I allergies, allergic rhinitis, and/or asthma. Onset is most common between 3 and 6 months of age, with approximately 60% of patients developing the eruption in the first year of life and 90% by age 5. While the majority of affected individuals have resolution of disease by adulthood, 10 to 30% do not, and a smaller percentage first develop symptoms as adults. AD has a complex pathogenesis involving genetic, immunologic, and environmental factors, which lead to a dysfunctional skin barrier and dysregulation of the immune system. Clinical findings include erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and lichenification. These clinical findings vary by patient age and chronicity of lesions. Pruritus is a hallmark of the condition that is responsible for much of the disease burden borne by patients and their families. Typical patterns include facial, neck and extensor involvement in infants and children; flexure involvement in any age group, with sparing of groin and axillary regions.[2]

Goals of treatment are to reduce symptoms (pruritus and dermatitis), prevent exacerbations, and minimize therapeutics risks.[13] Despite its relapsing and remitting nature, the majority of patients with AD can achieve clinical improvement and disease control with nonpharmacological interventions (e.g., emollient use), conventional topical therapies (including corticosteroids and calcineurin inhibitors) and environmental and occupational modifications, when necessary.[4,5,13] The American Academy of Dermatology (AAD) guidelines suggest application of moisturizers should be an integral part of the treatment of patients with AD as there is strong evidence that their use reduces disease severity and need for pharmacologic intervention. They are an important component of maintenance treatment and prevention of flares.[4] The AAD recommends topical corticosteroids (TCS) for patients who fail to respond to good skin care and regular use of emollients alone. Proactive, intermittent use of topical corticosteroids as maintenance therapy (1-2 times weekly) on areas that commonly flare is recommended to help prevent relapses and is more effective than use of emollients alone. Monitoring by physical exam for cutaneous side effects during long-term, potent steroid use is suggested. Proactive, once to twice weekly application of mid-potency TCS for up to 40 weeks has not demonstrated adverse events (e.g., purpura, telangiectasia, striae, focal hypertrichosis, acneiform/rosacea-like eruptions, skin atrophy) in clinical trials.[4] It is recommended that patients with acute flares use super high or high potency topical corticosteroids for one to two weeks, and then replace these with lower potency preparations until the lesions resolve.[14] AAD notes that mid- to higher potency topical corticosteroids are appropriate for short courses to gain rapid control of symptoms, but long-term management should use the least-potent corticosteroid that is effective.[4] In general, if AD is not responding after 2 weeks of treatment, evaluation to determine other treatment plans is indicated.[3,14]

Topical calcineurin inhibitors (TCIs) (e.g., pimecrolimus, tacrolimus) are recommended by the AAD as second-line therapy and are effective for acute and chronic treatment. They are particularly useful in selected clinical situations such as recalcitrance to steroids; for sensitive areas (face, anogenital, skin folds); for steroid-induced atrophy; and when there is long-term

uninterrupted topical steroid use. TCIs are recommended for use on actively affected areas as a steroid-sparing agent. Proactive, intermittent use of TCIs as maintenance therapy (2-3 times per week) on areas that commonly flare is recommended to help prevent relapses while reducing need for topical corticosteroids and is more effective than use of emollients alone.[4] Prescribing information for Elidel® (pimecrolimus) cream and Protopic® (tacrolimus) ointment indicate evaluation after 6 weeks if symptoms of AD do not improve for adults and pediatrics.[6,12]

Phototherapy is recommended as a treatment for both acute and chronic AD in children and adults, after failure of the mentioned above. Systemic immunomodulator agents are indicated and recommended for the subset of adult and pediatric patients in whom optimized topical regimens using emollients, topical anti-inflammatory therapies, adjunctive methods, and/or phototherapy do not adequately control the signs and symptoms of disease. Photo therapy and systemic immunomodulating agents may also be used in patients whose medical, physical, and/or psychological states are greatly affected by their skin disease. Oral cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil are the most commonly used systemic immunomodulators and most efficacious for treating AD. The AAD recommends that systemic corticosteroids should be avoided if possible and should exclusively be reserved for acute, severe exacerbations and as a short-term bridge to other systemic, steroid sparing therapies.[5,18]

Efficacy[1,7,8]

Dupilumab was FDA approved through two randomized, double-blind, placebo-controlled phase 3 trials (SOLO 1 and SOLO 2). All patients in both trials were at least 18 years old, had chronic AD (according to American Academy of Dermatology Consensus Criteria Eichenfield 2014) that had been present for at least 3 years, and had greater than or equal to 10% body surface area (BSA) involvement at the screening and baseline visits. Additionally, all patients had a documented recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications (defined as failure to achieve and maintain remission or a low disease activity state despite treatment with a daily regimen of topical corticosteroids of medium to higher potency applied for ≥28 days or for the maximum duration recommended by the product prescribing information [e.g., 14 days for super-potent topical corticosteroids], whichever is shorter), or whom topical treatments are otherwise medically inadvisable. The primary outcome measure in both trails was proportion of patients with both IGA (Investigator Global Assessment) 0 to 1 (on a 5-point scale) and a reduction from baseline of greater than or equal to 2 points at week 16. There were several secondary endpoints included. Some examples include: proportion of patients with Eczema Area and Severity Index (EASI) -75 (greater than or equal to 75% improvement from baseline) at week 16, percent change from baseline to week 16 in pruritus numerical rating scale (NRS), change from baseline to week 16 in % BSA, and changes in quality of life, anxiety, and depression.

The manufacturer reports the following results from SOLO 1 and SOLO 2. In SOLO 1, the primary outcome (an IGA of 0-1 and a reduction of greater than or equal to 2 points from baseline at week 16) occurred in 85 patients (38%) who received dupilumab every other week and in 83 (37%) who received dupilumab weekly, as compared with 23 (10%) who received placebo (P less than 0.001 for both comparisons with placebo). The results were similar in SOLO 2, with the primary outcome occurring in 84 patients (36%) who received dupilumab every other week and in 87 (36%) who received dupilumab weekly, as compared with 20 (8%) who received placebo (P less than 0.001 for both comparisons). In addition, in the two trials, an improvement from baseline to week 16 of at least 75% on the Eczema Area and Severity Index was reported in significantly more patients who received each regimen of dupilumab than in patients who received placebo (P less than 0.001 for all comparisons). Dupilumab was also associated with improvement in other clinical end points, including

reduction in pruritus and symptoms of anxiety or depression and improvement in quality of life.

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 AD and a minimum BSA involvement of greater than or equal to 10%. Eligible subjects enrolled into this trial had previous inadequate response to topical medication. Subjects in the Dupixent group with baseline weight of less than 60 kg received an initial dose of 400 mg at Week 0, followed by 200 mg Q2W for 16 weeks. Subjects with baseline weight of greater than or equal to 60 kg received an initial dose of 600 mg at Week 0, followed by 300 mg Q2W for 16 weeks. Subjects were permitted to receive rescue treatment at the discretion of the investigator. Subjects who received rescue treatment were considered non-responders. 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. Other evaluated outcomes included the proportion of subjects with EASI-75 or EASI-90 (improvement of at least 75% or 90% in EASI from baseline, respectively), and reduction in itch as measured by the Peak Pruritus NRS (≥4-point improvement).

The efficacy results at Week 16 were as follows:

- IGA 0 or 1: 24% for Dupixent and 2% for placebo
- EASI-75: 42% for Dupixent and 8% for placebo
- EASI-90: 23% for Dupixent and 2% for placebo
- Peak Pruritus NRS (greater than or equal to 4-point improvement): 37% for Dupixent and 5% for placebo

Asthma

Asthma is a chronic inflammatory disorder of the airways.[9,11] It is characterized by variable and recurring clinical symptoms, airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation.[9] Symptoms of asthma include wheezing, coughing, recurrent difficulty breathing, shortness of breath, and chest tightness. Generally, these symptoms will occur or worsen with exposure to allergens and irritants, infections, exercise, changes in weather, stress, or menstrual cycles. Guidelines recommend the use of detailed medical history, physical examination, and spirometry to make a diagnosis of asthma. In addition, differential diagnosis of asthma should be considered.[9,11]

The Global Initiative for Asthma (GINA) guidelines recommend a stepwise approach for managing asthma.[11] Long-term goals for asthma management are to achieve good control of symptoms, maintain normal activity level, and to minimize the future risk of exacerbations, fixed airflow limitation, and side-effects.[10] IgE is the antibody responsible for activation of allergic reactions and is important to the pathogenesis of allergic asthma and the development and persistence of inflammation. GINA guidelines define moderate asthma as that which is well controlled with low dose inhaled corticosteroids (ICS) in combination with a long acting beta agonist (LABA). Severe asthma is defined as asthma that requires Step 4 or 5 treatment (e.g., with high dose ICS plus a LABA) to prevent it from becoming 'uncontrolled' or which remains uncontrolled despite this therapy. Early initiation of low dose ICS in patients with asthma has led to greater improvement in lung function than initiation of ICS after symptoms have been present for more than 2 to 4 years. The 2021 GINA guidelines recommend every adult and adolescent with asthma should receive ICS-containing controller medication to reduce the risk of serious exacerbation, even in patients with infrequent symptoms.[11]

2021 GINA STEP recommendations for adults and adolescents (12 years of age and over) are intended to reduce the risk of serious exacerbations. 2021 GINA guidelines have been updated to include two treatment "tracks", with the key difference being the medication that

is used for symptoms relief: as-needed low dose ICS-formoterol in Track 1, and as-needed SABA in Track 2.[11]

Track 1 is the preferred approach recommended by GINA, because using low dose ICS-formoterol as reliever reduces the risk of severe exacerbations compared with regimens with SABA as reliever, with similar symptom control:[11]

- Steps 1 and 2: As-needed low dose ICS-formoterol
  - Alternative options: Daily leukotriene receptor antagonist (LTRA), or add house dust mite (HDM) sublingual immunotherapy (SLIT)
- Step 3: Low dose maintenance ICS-formoterol
  - Reliever: As-needed low dose ICS-formoterol
  - Alternative options: Medium dose ICS, or add LTRA, or add HDM SLIT
- Step 4: Medium dose maintenance ICS-formoterol
  - Reliever: As-needed low dose ICS-formoterol
  - Alternative options: Add long-acting muscarinic antagonist (LAMA) or LTRA, or switch to high dose ICS
- Step 5: Add-on LAMA; refer for phenotypic assessment and consideration of anti-IgE, anti-IL5/5R, anti-IL4R; consider high dose ICS-formoterol
  - Reliever: As-needed low dose ICS-formoterol
  - Alternative options: Add azithromycin (adults) or LTRA; add low dose oral corticosteroids (OCS) but consider side effects

Track 2 is an alternative approach if Track 1 is not possible or is not preferred by a patient with no exacerbations on their current therapy. Before considering a regimen with SABA reliever, the clinician should consider whether the patient is likely to be adherent with their controller therapy; if not, they will be exposed to the risks of SABA-only treatment:[11]

- Step 1: Take ICS whenever SABA taken
  - Reliever: As-needed short-acting β-2 agonist (SABA)
- Step 2: Low dose maintenance ICS
  - Reliever: As-needed SABA
  - Alternative options: Low dose ICS whenever SABA taken, or daily LTRA, or add HDM SLIT
- Step 3: Low dose maintenance ICS-LABA
  - Reliever: As-needed SABA
  - Alternative options: Medium dose ICS, or add LTRA, or add HDM SLIT
- Step 4: Medium/high dose maintenance ICS-LABA
  - Reliever: As-needed SABA
  - Alternative options: Add LAMA or LTRA, or switch to high dose ICS
- Step 5: Add-on LAMA; refer for phenotypic assessment and consideration of anti-IgE, anti-IL5/5R, anti-IL4R; consider high dose ICS-LABA
  - Reliever: As-needed SABA
  - Alternative options: Add azithromycin (adults) or LTRA; add low dose oral corticosteroids (OCS) but consider side effects

2021 GINA STEP recommendations for children (6 to 11 years of age) are intended to reduce the risk of serious exacerbations:[11]

- Step 1:
  - Possible controller: as needed ICS taken at the same time as a SABA OR regular low dose ICS with as needed SABA (likelihood of poor adherence should be taken into account)
- Step 2:
  - Preferred controller: daily low dose ICS with as needed SABA
  - Alternative options: Leukotriene receptor antagonist (LTRA) or as needed ICS taken at the same time as a SABA
  - LTRA are less effective than ICS, particularly for preventing exacerbations

- Step 3:
    - Address and treat modifiable risk factors (e.g., adherence, technique)
    - Preferred controller:
        - Daily medium dose ICS with as-needed SABA as reliever, or
        - Change to a combination low dose ICS-LABA plus as-needed SABA, or
        - Maintenance and reliever therapy (MART) with very low dose ICS-formoterol
- Step 4:
    - Medium dose ICS-LABA, or
    - MART with low dose budesonide-formoterol
    - Alternative options: high dose ICS-LABA; add-on tiotropium
- Step 5:
    - Refer for expert assessment and advice if not controlled on a moderate dose ICS
    - Alternative options: add-on tiotropium

Severe Asthma Phenotype and Eosinophilic Asthma Subphenotype
Severe asthma is defined by GINA guidelines as asthma that is uncontrolled despite adherence with maximal optimized GINA Step 4 or Step 5 therapy (e.g., medium or high dose ICS with a second controller; maintenance OCS) and treatment of contributory factors (e.g., inhaler technique, smoking or comorbidities), or that worsens when high dose treatment is decreased. Roughly 3% to 10% of adults with asthma have severe asthma.[11] The European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (2014; updated 2020) mirror the GINA definition of severe asthma, and defined uncontrolled asthma as:[9]

- Frequent severe exacerbations (i.e., two or more bursts of systemic corticosteroids within the past 12 months)
- Serious exacerbations (i.e., at least one hospitalization, intensive care unit stay, or mechanical ventilation in the past 12 months)
- Airflow limitation (i.e., FEV1 less than 80% predicted)
- Asthma that worsens upon tapering of high-dose ICS or systemic corticosteroids

A specialist, preferably in a multidisciplinary severe asthma clinic (if available) performs further assessment, which includes the patient's inflammatory phenotype (i.e., Type 2 or non-Type 2).[11]

Type 2 inflammation is characterized by the presence of cytokines such as interleukin (IL)-4, IL-5, and IL-13, which are often produced by the adaptive immune system on recognition of allergens. It is also characterized by eosinophilia or increased fraction of exhaled nitric oxide (FeNO) and may be accompanied by atopy. In many patients with asthma, Type 2 inflammation rapidly improves when ICS are taken regularly and correctly; this is classified as mild or moderate asthma. In severe asthma, Type 2 inflammation may be relatively refractory to high dose ICS. Type 2 inflammation is considered refractory if any of the following are found while the patient is taking high dose ICS or daily OCS:

- Blood eosinophils greater than or equal to 150 cells/microliter
- FeNO greater than or equal to 20 ppb
- Sputum eosinophils greater than or equal to 2%
- Asthma is clinically allergen-driven

Biologic agents should be considered as add-on therapy for patients with refractory Type 2 inflammation with exacerbations or poor symptom control despite taking at least high dose ICS/LABA, and who have allergic or eosinophilic biomarkers or need maintenance OCS.[11]

Efficacy[1]

The asthma development program included three randomized, double-blind, placebo controlled, parallel-group, multi-center trials (AS Trials 1, 2, and 3) of 24 to 52 weeks in treatment duration which enrolled a total of 2888 subjects (12 years of age and older). Subjects enrolled in AS Trials 1 and 2 were required to have a history of 1 or more asthma exacerbations that required treatment with systemic corticosteroids or emergency department visit or hospitalization for the treatment of asthma in the year prior to trial entry. Subjects enrolled in AS Trial 3 required dependence on daily oral corticosteroids in addition to regular use of high-dose inhaled corticosteroids plus an additional controller(s). In all 3 trials, subjects were enrolled without requiring a minimum baseline blood eosinophil count. In AS Trials 2 and 3 subjects with screening blood eosinophil level of >1500 cells/mcL (less than 1.3%) were excluded. Dupixent was administered as add-on to background asthma treatment. Subjects continued background asthma therapy throughout the duration of the studies, except in AS Trial 3 in which OCS dose was tapered as described below.

AS Trial 1 was a 24-week dose-ranging study which included 776 subjects (18 years of age and older). Dupixent compared with placebo was evaluated in adult subjects with moderate to severe asthma on a medium or high-dose inhaled corticosteroid and a long acting beta agonist. Subjects were randomized to receive either 200 mg (N=150) or 300 mg (N=157) Dupixent every other week (Q2W) or 200 mg (N=154) or 300 mg (N=157) Dupixent every 4 weeks following an initial dose of 400 mg, 600 mg or placebo (N=158), respectively. The primary endpoint was mean change from baseline to Week 12 in FEV1 (L) in subjects with baseline blood eosinophils greater than or equal to 300 cells/mcL. Other endpoints included percent change from baseline in FEV1 and annualized rate of severe asthma exacerbation events during the 24-week placebo controlled treatment period. Results were evaluated in the overall population and subgroups based on baseline blood eosinophil count (greater than or equal to 300 cells/mcL and less than 300 cells/mcL. Additional secondary endpoints included responder rates in the patient reported Asthma Control Questionnaire (ACQ-5) and Asthma Quality of Life Questionnaire, Standardized Version (AQLQ(S)) scores.

AS Trial 2 was a 52-week study which included 1902 subjects (12 years of age and older). Dupixent compared with placebo was evaluated in 107 adolescents and 1795 adult subjects with moderate-to-severe asthma on a medium or high-dose inhaled corticosteroid (ICS) and a minimum of one and up to two additional controller medications. Subjects were randomized to receive either 200 mg (N=631) or 300 mg (N=633) Dupixent Q2W (or matching placebo for either 200 mg [N=317] or 300 mg [N=321] Q2W) following an initial dose of 400 mg, 600 mg or placebo respectively. The primary endpoints were the annualized rate of severe exacerbation events during the 52-week placebo-controlled period and change from baseline in pre-bronchodilator FEV1 at Week 12 in the overall population (unrestricted by minimum baseline blood eosinophils count). Additional secondary endpoints included annualized severe exacerbation rates and FEV1 in patients with different baseline levels of blood eosinophils as well as responder rates in the ACQ-5 and AQLQ(S) scores.

AS Trial 3 was a 24-week oral corticosteroid-reduction study in 210 subjects with asthma who required daily oral corticosteroids in addition to regular use of high dose inhaled corticosteroids plus an additional controller. After optimizing the OCS dose during the screening period, subjects received 300 mg Dupixent (N=103) or placebo (N=107) once Q2W for 24 weeks following an initial dose of 600 mg or placebo. Subjects continued to receive their existing asthma medicine during the study; however, their OCS dose was reduced every 4 weeks during the OCS reduction phase (Week 4-20), as long as asthma control was maintained. The primary endpoint was the percent reduction of oral corticosteroid dose at Weeks 20 to 24 compared with the baseline dose, while maintaining asthma control in the overall population (unrestricted by minimum baseline blood eosinophils count). Additional secondary endpoints included the annualized rate of severe exacerbation events during treatment period and responder rate in the ACQ-5 and AQLQ(S) scores.

AS Trials 1 and 2 evaluated the frequency of severe asthma exacerbations defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or hospitalization or emergency room visit due to asthma that required systemic corticosteroids. In the primary analysis population (subjects with baseline blood eosinophil count of greater than or equal to 300 cells/mcL in AS Trial 1 and the overall population in AS Trial 2), subjects receiving either Dupixent 200 mg or 300 mg Q2W had significant reductions in the rate of asthma exacerbations compared to placebo. In the overall population in AS Trial 2, the rate of severe exacerbations was 0.46 and 0.52 for Dupixent 200 mg Q2W and 300 mg Q2W, respectively, compared to matched placebo rates of 0.87 and 0.97. The rate ratio of severe exacerbations compared to placebo was 0.52 (95% CI: 0.41, 0.66) and 0.54 (95% CI: 0.43, 0.68) for Dupixent 200 mg Q2W and 300 mg Q2W, respectively.

Prespecified subgroup analyses of AS Trials 1 and 2 demonstrated that there were greater reductions in severe exacerbations in subjects with higher baseline blood eosinophil levels. In AS Trial 2, reductions in exacerbations were significant in the subgroup of subjects with baseline blood eosinophils greater than or equal to 150 cells/mcL. In subjects with baseline blood eosinophil count less than 150 cells/mcL, similar severe exacerbation rates were observed between Dupixent and placebo.

Significant increases in pre-bronchodilator FEV1 were observed at Week 12 for AS Trials 1 and 2 in the primary analysis populations (subjects with baseline blood eosinophil count of greater than or equal to 300 cells/mcL in AS Trial 1 and the overall population in AS Trial 2). In the overall population in AS Trial 2, the FEV1 LS mean change from baseline was 0.32 L (21%) and 0.34 L (23%) for Dupixent 200 mg Q2W and 300 mg Q2W, respectively, compared to matched placebo means of 0.18 L (12%) and 0.21 L (14%). The mean treatment difference versus placebo was 0.14 L (95% CI: 0.08, 0.19) and 0.13 L (95% CI: 0.08, 0.18) for Dupixent 200 mg Q2W and 300 mg Q2W, respectively. Subgroup analysis of AS Trials 1 and 2 demonstrated greater improvement in subjects with higher baseline blood eosinophils.

Chronic Rhinosinusitis with Nasal Polyposis

Chronic rhinosinusitis with nasal polyposis (CRSwNP) is an inflammatory condition affecting the paranasal sinuses. Hallmarks of the disease consist of at least two out of four cardinal symptoms (i.e., facial pain/pressure, hyposmia/anosmia, nasal drainage, and nasal obstruction) for at least 12 consecutive weeks in addition to nasal polyps and sinonasal inflammation.[15-17] Sinus computed tomography (CT) and/or nasal endoscopy are needed to determine the presence of sinonasal inflammation and nasal polyps. The exact cause of CRSwNP is unknown, but biopsies of nasal polyps have shown elevated levels of eosinophils.[15]

First line therapy for CRSwNP consists of nasal saline irrigation in combination with intranasal corticosteroids.[15-17] The American Academy of Family Physicians notes that no one intranasal corticosteroid is superior to another or that increased dosing provides greater effectiveness. The American Academy of Otolaryngology recommends a short course of oral corticosteroids if no response is seen with intranasal corticosteroids after 3-months of appropriate use.[17] Short courses of oral corticosteroids (up to three weeks) can improve sinonasal symptoms and endoscopic findings. Surgical intervention may be required in patients in which medical therapy is ineffective.[15,16]

Efficacy[1]

Two randomized, double-blind, parallel-group, multicenter, placebo-controlled studies (CSNP Trial 1 and CSNP Trial 2) evaluated Dupixent in CRSwNP. There were 724 subjects aged 18 years and older on background intranasal corticosteroids (INCS) included in the trials. These studies included subjects with CRSwNP despite prior sinonasal 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. 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 sinonasal outcome test (SNOT-22). In the pooled efficacy results, the reduction in the proportion of subjects rescued with systemic corticosteroids and/or sinonasal surgery (up to Week 52) were evaluated.

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. In both studies, significant improvements in nasal congestion were observed as early as the first assessment at Week 4. A significant decrease in the LMK sinus CT scan score was observed. Dupilumab significantly improved the loss of smell compared to placebo. In both studies, significant improvements in daily loss of smell severity were observed as early as the first assessment at Week 4. Dupilumab significantly decreased sinonasal symptoms as measured by SNOT-22 compared to placebo.

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 sinonasal 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).

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.

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Interleukin-4 (IL-4) Inhibitor Prior Authorization with Quantity Limit

TARGET AGENT(S)
Dupixent® (dupilumab)

Brand (generic)	GPI	Multisource Code	Quantity Limit (per day or as listed)
Dupixent (dupilumab)			
100 mg/0.67 mL pre-filled syringe	9027302000E510	M, N, O, or Y	2 syringes (1.34 mL)/ 28 days
200 mg/1.14 mL pre-filled syringe	9027302000E515	M, N, O, or Y	2 syringes (2.28 mL)/ 28 days
300 mg/2 mL pre-filled syringe	9027302000E520	M, N, O, or Y	2 syringes (4 mL)/ 28 days
200 mg/1.14 mL pre-filled pen injector	9027302000D215	M, N, O, or Y	2 pens (2.28 mL)/ 28 days
300 mg/2 mL pre-filled pen injector	9027302000D220	M, N, O, or Y	2 pens (4 mL)/ 28 days

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Initial Evaluation
Target Agent(s) will be approved when ALL of the following are met:
1. ONE of the following:
    A. The requested agent is eligible for continuation of therapy AND ONE of the following:
        i. Information has been provided that indicates the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days
        OR
        ii. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed

Agents Eligible for Continuation of Therapy
All target agents are eligible for continuation of therapy

    OR
    B. The patient has a diagnosis of moderate-to-severe atopic dermatitis AND ALL of the following:
        i. ONE of the following:
            a. The patient has at least 10% body surface area involvement
            OR
            b. The patient has involvement of the palms and/or soles of the feet
        AND
        ii. ONE of the following:
            a. The patient has tried and had an inadequate response after a minimum of 3 months with an oral systemic immunosuppressant (e.g., methotrexate, azathioprine, mycophenolate mofetil, cyclosporine)
            OR
            b. The patient has an intolerance or hypersensitivity to an oral systemic immunosuppressant
            OR

c. The patient has tried and had an inadequate response to BOTH at least a mid-potency topical steroid used for a minimum of 4 weeks AND a topical calcineurin inhibitor (e.g., Elidel/pimecrolimus, Protopic/tacrolimus) used for a minimum of 6 weeks
OR
d. The patient has an intolerance or hypersensitivity to BOTH at least a mid-potency topical steroid AND a topical calcineurin inhibitor
OR
e. The patient has an FDA labeled contraindication to ALL oral systemic immunosuppressants, mid-potency topical steroids, AND topical calcineurin inhibitors

AND

iii. The prescriber has assessed the patient's baseline (prior to therapy with the requested agent) pruritus and other symptom severity (e.g., erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and/or lichenification)
AND
iv. ONE of the following:
a. The patient will be using standard maintenance therapy (e.g., topical emollients, good skin care practices) in combination with the requested agent
OR
b. The patient has an intolerance, hypersensitivity, or FDA labeled contraindication to ALL standard maintenance therapies

OR

C. The patient has a diagnosis of moderate to severe asthma AND ALL of the following:
i. ONE of the following:
a. The patient has eosinophilic type asthma AND ONE of the following:
1. The patient has a baseline (prior to therapy with the requested agent) blood eosinophilic count of 150 cells/microliter or higher while on high-dose inhaled corticosteroids or daily oral corticosteroids
OR
2. The patient has sputum eosinophils 2% or higher while on high-dose inhaled corticosteroids or daily oral corticosteroids
OR
b. The patient has oral corticosteroid dependent type asthma

AND

ii. The patient has a history of uncontrolled asthma while on asthma control therapy as demonstrated by ONE of the following:
a. Frequent severe asthma exacerbations requiring two or more courses of systemic corticosteroids (steroid burst) within the past 12 months
OR
b. Serious asthma exacerbations requiring hospitalization, mechanical ventilation, or visit to the emergency room or urgent care within the past 12 months
OR
c. Controlled asthma that worsens when the doses of inhaled and/or systemic corticosteroids are tapered

OR

d. The patient has baseline (prior to therapy with the requested agent) Forced Expiratory Volume (FEV1) that is less than 80% of predicted

AND

iii. ONE of the following:
   a. The patient is NOT currently being treated with the requested agent AND is currently treated with a maximally tolerated inhaled corticosteroid for at least 3 months
   OR
   b. The patient is currently being treated with the requested agent AND ONE of the following:
      1. Is currently treated with an inhaled corticosteroid for at least 3 months that is adequately dosed to control symptoms
      OR
      2. Is currently treated with a maximally tolerated inhaled corticosteroid for at least 3 months
   OR
   c. The patient has an intolerance or hypersensitivity to inhaled corticosteroid therapy
   OR
   d. The patient has an FDA labeled contraindication to ALL inhaled corticosteroids

AND

iv. ONE of the following:
   a. The patient is currently being treated for at least 3 months with ONE of the following:
      1. A long-acting beta-2 agonist (LABA)
      OR
      2. A leukotriene receptor antagonist (LTRA)
      OR
      3. Long-acting muscarinic antagonist (LAMA)
      OR
      4. Theophylline
   OR
   b. The patient has an intolerance or hypersensitivity to therapy with LABA, LTRA, LAMA, or theophylline
   OR
   c. The patient has an FDA labeled contraindication to ALL LABA, LTRA, LAMA, AND theophylline therapies

AND

v. The patient will continue asthma control therapy (e.g., ICS, LABA, LTRA, LAMA, theophylline) in combination with the requested agent

OR

D. The patient has a diagnosis of chronic rhinosinusitis with nasal polyposis (CRSwNP) AND ALL of the following:
   i. There is information indicating the patient's diagnosis was confirmed by ONE of the following:
      a. Anterior rhinoscopy or endoscopy
      OR
      b. Computed tomography (CT) of the sinuses

   AND

   ii. ONE of the following:
      a. ONE of the following:

1. The patient had an inadequate response to sinonasal surgery
   OR
2. The patient is NOT a candidate for sinonasal surgery

OR

b. ONE of the following:
   1. The patient has tried and had an inadequate response to oral systemic corticosteroids
      OR
   2. The patient has an intolerance or hypersensitivity to therapy with oral systemic corticosteroids
      OR
   3. The patient has an FDA labeled contraindication to ALL oral systemic corticosteroids

AND

iii. ONE of the following:
   a. The patient has tried and had an inadequate response to intranasal corticosteroids (e.g., fluticasone, Sinuva) used for at least a 3-month trial
      OR
   b. The patient has an intolerance or hypersensitivity to therapy with intranasal corticosteroids (e.g., fluticasone, Sinuva)
      OR
   c. The patient has an FDA labeled contraindication to ALL intranasal corticosteroids

AND

iv. BOTH of the following:
   a. The patient is currently treated with standard nasal polyp maintenance therapy (e.g., nasal saline irrigation, intranasal corticosteroids)
      AND
   b. The patient will continue standard nasal polyp maintenance therapy (e.g., nasal saline irrigation, intranasal corticosteroids) in combination with the requested agent

OR

E. The patient has another FDA approved indication for the requested agent and route of administration
   OR
F. The patient has another indication that is supported in compendia for the requested agent and route of administration

AND

2. ONE of the following:
   A. The patient's age is within FDA labeling for the requested indication for the requested agent
      OR
   B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication

AND

3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., atopic dermatitis -dermatologist, allergist, immunologist; asthma -allergist, immunologist, pulmonologist; CRSwNP -otolaryngologist, allergist, pulmonologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis

AND

4. The patient will NOT be using the requested agent in combination with another biologic agent for the requested indication [e.g., Opzelura, Xolair, IL-5 inhibitor (Cinqair, Fasenra, Nucala)]
   AND
5. The patient does NOT have any FDA labeled contraindications to the requested agent
   AND
6. ONE of the following:
   A. The requested quantity (dose) does NOT exceed the program quantity limit
      OR
   B. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit
         AND
      ii. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose, or the compendia supported dose, for the requested indication
         AND
      iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

Compendia Allowed: AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use

Length of Approval: 6 months
Note: Please approve initial loading dose for asthma and atopic dermatitis only
- 300 mg strength requested: 600 mg (two 300 mg injections) followed by maintenance dose
- 200 mg strength requested: 400 mg (two 200 mg injections) followed by maintenance dose

Renewal Evaluation
Target Agent(s) will be approved when ALL of the following are met:
1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process
   AND
2. ONE of the following:
   A. The patient has a diagnosis of moderate-to-severe atopic dermatitis AND BOTH of the following:
      i. The patient has had a reduction or stabilization from baseline (prior to therapy with the requested agent) of ONE of the following:
         a. Affected body surface area
            OR
         b. Flares
            OR
         c. Pruritus, erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and/or lichenification
      AND
      ii. The patient will continue standard maintenance therapies (e.g., topical emollients, good skin care practices) in combination with the requested agent
   OR
   B. The patient has a diagnosis of moderate to severe asthma AND BOTH of the following:

i. The patient has had improvements or stabilization with the requested agent from baseline (prior to therapy with the requested agent) as indicated by ONE of the following:
   a. The patient has had an increase in percent predicted Forced Expiratory Volume (FEV_1)
      OR
   b. The patient has had a decrease in the dose of inhaled corticosteroids required to control the patient's asthma
      OR
   c. The patient has had a decrease in need for treatment with systemic corticosteroids due to exacerbations of asthma
      OR
   d. The patient has had a decrease in number of hospitalizations, need for mechanical ventilation, or visits to urgent care or emergency room due to exacerbations of asthma

AND

ii. The patient is currently treated and is compliant with asthma control therapy [e.g., inhaled corticosteroids, long-acting beta-2 agonist (LABA), leukotriene receptor antagonist (LTRA), long-acting muscarinic antagonist (LAMA), theophylline]

OR

C. The patient has a diagnosis of chronic rhinosinusitis with nasal polyposis (CRSwNP) AND BOTH of the following:
   i. The patient has had clinical benefit with the requested agent
      AND
   ii. The patient will continue standard nasal polyp maintenance therapy (e.g., nasal saline irrigation, intranasal corticosteroids) in combination with the requested agent

OR

D. The patient has another FDA approved indication for the requested agent and route of administration AND has had clinical benefit with the requested agent

OR

E. The patient has another indication that is supported in compendia for the requested agent and route of administration AND has had clinical benefit with the requested agent

AND

3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., atopic dermatitis -dermatologist, allergist, immunologist; asthma -allergist, immunologist, pulmonologist; CRSwNP -otolaryngologist, allergist, pulmonologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis

AND

4. The patient will NOT be using the requested agent in combination with another biologic agent for the requested indication [e.g., Opzelura, Xolair, IL-5 inhibitor (Cinqair, Fasenra, Nucala)]

AND

5. The patient does NOT have an FDA labeled contraindications to the requested agent

AND

6. ONE of the following:
   A. The requested quantity (dose) does NOT exceed the program quantity limit
      OR
   B. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit
         AND

ii. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose, or the compendia supported dose, for the requested indication
AND
iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

Compendia Allowed: AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use

Length of Approval: 12 months