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Prior Authorization Criteria Update: Dupilumab

Purpose of Update:

Dupilumab was recently reviewed by the Pharmacy and Therapeutics (P and T) Committee at the July 2019 meeting. To support administration of PA criteria, dupilumab was removed from atopic dermatitis (AD) and topical antipsoriatic prior authorization (PA) criteria and a new PA document to support dupilumab utilization in moderate-to-severe asthma and moderate-to-severe AD was approved. In June 2019, dupilumab received Food and Drug Administration (FDA) approval as add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP).[1] Chronic sinusitis is funded condition on line 463 of the Oregon Health Evidence Review Commission's prioritized list of health conditions.[2] This update evaluates evidence for dupilumab use in CRSwNP.

Background:

Chronic rhinosinusitis with nasal polyposis (CRSwNP) is an inflammatory disease of the nasal and paranasal mucosa, which causes symptoms of nasal obstruction, decreased sense of smell, facial pain, headache, and rhinorrhea. Typically observed in the context of eosinophilic inflammation of the upper airways, nasal polyps originate in the sinuses and obstruct the sinus and nasal passages.[3] Therapy for CRSwNP includes nasal saline irrigations and intranasal corticosteroid sprays for maintenance therapy, and systemic corticosteroids with antibiotics for acute exacerbations.[4] If patients do not experience symptom relief, endoscopic sinus surgery may be considered in order to alleviate obstruction, remove inflammatory tissue, and facilitate delivery of topical therapies.[4] Research has been directed toward a better understanding of the inflammatory pathways in CRSwNP so that more targeted biologic therapies can be developed. Omalizumab, mepolizumab, and reslizumab are currently being studied as treatment options in adults with CRSwNP.

The FDA approved dupilumab as add-on maintenance treatment in adults patients with inadequately controlled CRSwNP based on data from 1 randomized controlled trial (RCT).[1] This trial was a randomized, double-blind, placebo-controlled, parallel-group study conducted at 13 sites in the United States and Europe in 60 adults aged 18 to 65 years with CRSwNP refractory to intranasal corticosteroids.[3] Patients were randomized to receive subcutaneous dupilumab (a 600 mg loading dose followed by 300 mg weekly (n = 30); or placebo (n = 30) plus mometasone furoate nasal spray twice daily for 16 weeks.[3] The primary endpoint was mean change in bilateral endoscopic nasal polyp score from baseline to week 16.[3] This score is graded based on polyp size (recorded as the sum of the right and left nostril scores with a range of 0-8; higher scores indicate worse status).[3] Of note, a minimal clinically important difference (MCID) for nasal polyp score has not yet been established.[3] Subjects enrolled in this trial were required to have a bilateral endoscopic nasal polyp score of at least 5 (maximum score of 8), with a score of at least 2 for each nostril, and have at least 2 of the following symptoms prior to screening: nasal obstruction or discharge, facial pain or pressure, and reduction or lost sense of smell.[3]

The least squares mean (LSM) change in bilateral endoscopic nasal polyp score between baseline and week 16 was −0.3 in the placebo group and −1.9 in the dupilumab group (LSM difference −1.6; 95% CI, −2.4 to −0.7; P<0.001).[3] Adverse events were reported by 25 of 30 patients in the placebo group and 30 of 30 in the dupilumab group.[3] Mild-to-moderate nasopharyngitis (33% in the placebo group vs. 47% in the dupilumab group), injection site reactions (7% vs. 40%,

respectively), and headache (17% vs. 20%, respectively) were the most frequently reported adverse events.[3] This was small trial of limited duration; therefore, there is insufficient evidence to assess the effect of long-term treatment of CRSwNP with dupilumab. The study was funded by Sanofi and Regeneron Pharmaceuticals. The manufacturers, in collaboration with the academic clinical investigators, provided input on the design and conduct of the study; oversaw the collection, management, and statistical analysis of data; and contributed to the interpretation of the data and the preparation, review, and submission of the manuscript.[3]

Data from 2 additional trials (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52) were published in September 2019. The 2 trials evaluated the safety and efficacy of dupilumab in treating adults with severe CRSwNP previously treated with systemic corticosteroids and/or surgery.[5] The trial design was similar for both studies: international, multicenter, randomized, double-blind, placebo-controlled, parallel-group assessment of dupilumab added to standard of care in adults with severe CRSwNP.[5] SINUS-24 was conducted in 67 centers in 13 countries (Bulgaria, Czechoslovakia, France, Germany, Hungary, Italy, the Netherlands, Poland, Romania, Ukraine, Russia, United Kingdom, and United States). Patients (n=276) in SINUS-24 were randomized 1:1 to receive either to subcutaneous dupilumab 300 mg or placebo every 2 weeks for 24 weeks. SINUS-52 was conducted in 117 centers in 14 countries (Argentina, Australia, Belgium, Canada, Chile, Israel, Mexico, Portugal, Russia, Spain, Sweden, Turkey, Japan, and United States).[5] Patients in SINUS-52 (N=448) were randomized 1:1:1 to dupilumab 300 mg every 2 weeks for 52 weeks, dupilumab 300 mg every 2 weeks for 24 weeks and then 300 mg every 4 weeks for the remaining 28 weeks, or placebo every 2 weeks for 52 weeks.[5] Inclusion criteria were similar to the first RCT that evaluated the use of dupilumab in treating patients with CRSwNP.

The co-primary endpoints in both studies were change from baseline in both endoscopic nasal polyp score and nasal congestion severity (based on monthly average of daily score recorded by patients) at week 24.[5] Change from baseline in nasal congestion severity was assessed by a visual analog scale (score 0-3).[5] In SINUS-24, the LSM change in bilateral endoscopic nasal polyp score between baseline and week 24 was 0.17 in the placebo group and −1.9 in the dupilumab group (LSM difference –2.06; 95% CI, –2.43 to –1.69; p<0.0001).[5] Similar results were observed in SINUS-52, as the LSM change in bilateral endoscopic nasal polyp score between baseline and week 24 was 0.1 in the placebo group and −1.7 in the dupilumab group (LSM difference–1.80; 95% CI, –2.10 to –1.51; p<0.0001).[5] The difference in nasal congestion or obstruction score favored dupilumab over placebo at week 24 in SINUS-24 (LSM difference −0.89; 95% CI, –1.07 to –0.71; p<0.0001) and SINUS-52 (LSM difference −0.87; 95% CI, –1.03 to –0.71; p<0·0001).[5]

The most common adverse events (nasopharyngitis, worsening of nasal polyps and asthma, headache, epistaxis, and injection-site erythema) were more frequent with placebo than dupilumab over the 24 week treatment period.[5] In SINUS-52, treatment-emergent adverse events of worsening of nasal polyps and asthma and of sinusitis, arthralgia, and accidental overdose occurred more frequently in patients who switched from dupilumab every 2 weeks to every 4 weeks than in those who remained on dupilumab every 2 weeks for the full 52 weeks.[5] Dupilumab as monotherapy for treating CRSwNP has not been evaluated. Both trials were funded by Sanofi and Regeneron Pharmaceuticals.

Recommendation:

- Revise dupilumab PA criteria to include CRSwNP as an FDA-approved indication for dupilumab as add on therapy to standard of care for CRSwNP (**Appendix 1**).

References:

1. Dupixent® (dupilumab) Prescribing Information. Bridgewater,NJ; Sanofi-Aventis. June 2019.
2. Oregon Health Authority, Oregon Health Evidence Review Commission. Prioritized List of Health Services. 1/1/2019. https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Prioritized-List.aspx. Accessed October 10, 2019.
3. Bachert C, Mannent L, Naclerio RM, et al. Effect of Subcutaneous Dupilumab on Nasal Polyp Burden in Patients With Chronic Sinusitis and Nasal Polyposis: A Randomized Clinical TrialSubcutaneous Treatment for Chronic Sinusitis With Nasal PolyposisSubcutaneous Treatment for Chronic Sinusitis With Nasal Polyposis. *Jama.* 2016;315(5):469-479.
4. Kartush AG, Schumacher JK, Shah R, Patadia MO. Biologic Agents for the Treatment of Chronic Rhinosinusitis With Nasal Polyps. *Am J Rhinol Allergy.* 2019;33(2):203-211.
5. Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet (London, England).* 2019.

Dupilumab

Goal(s):

- Promote use that is consistent with national clinical practice guidelines and medical evidence.

Length of Authorization:

- 6 months

Requires PA:

- Dupilumab (Dupixent)

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD 10 code.	
2. Is the diagnosis an OHP funded diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny, not funded by the OHP.
3. Is this a request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the product requested preferred?	**Yes:** Approve for length of treatment; maximum 1 year.	**No:** Go to #5

Approval Criteria		
5. Will the prescriber consider a change to a preferred product? **Message:** Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of preferred alternatives. Approve for length of treatment; maximum 1 year.	**No**: Go to # 6
6. Is the medication being prescribed by or in consultation with a dermatologist, otolaryngologist, or allergist who specializes in management of severe asthma?	**Yes:** Go to # 7	**No:** Pass to RPh. Deny; medical appropriateness
7. What is the age of the patient? • Dupilumab injection is FDA approved for patients 12 years of age and older	**Age 11 years or younger**: Pass to RPh. Deny; medical appropriateness.	**Ages 12 years and older:** Go to #8
8. Is the diagnosis Moderate/Severe Atopic Dermatitis (AD)?	**Yes:** Go to #9	**No:** Go to #10

Approval Criteria		
9. Does the patient have a documented contraindication or failed trial of the following treatments: • Moderate to high potency topical corticosteroid (e.g., clobetasol, desoximetasone, desonide,mometasone, betamethasone, halobetasol, fluticasone, or fluocinonide) AND • Topical calcineurin inhibitor (tacrolimus, pimecrolimus) or topical phosphodiesterase (PDE)-4 inhibitor (crisaborole) AND • Oral immunomodulator therapy (cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, or oral corticosteroids)?	**Yes**: Document drug and dates trialed and intolerances (if applicable): 1._____(dates) 2._____(dates) 3._____(dates) Approve for length of treatment; maximum 6 months.	**No**: Pass to RPh. Deny; medical appropriateness
10. Is the claim for moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma?	**Yes:** Go to #11	**No:** ~~Pass to RPh. Deny; medical appropriateness~~ Go to # 14
11. Is the patient currently receiving another monoclonal antibody for asthma (e.g., omalizumab, mepolizumab, benralizumab or reslizumab)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #12
12. Has the patient required at least 1 hospitalization or ≥ 2 ED visits in the past 12 months while receiving a maximally-dosed inhaled corticosteroid (Table 1) AND 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, theophylline)?	**Yes:** Go to #13 Document number of hospitalizations or ED visits in past 12 months: _____. This is the baseline value to compare to in renewal criteria.	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
13. Has the patient been adherent to current asthma therapy in the past 12 months?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness.
14. Does the patient have chronic rhinosinusitis with nasal polyposis?	**Yes:** Go to # 15	**No:** Pass to RPh. Deny; medical appropriateness.
15. Has the patient failed medical therapy with inhaled corticosteroids (2 or more courses of adequate doses)?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is the request to renew dupilumab for atopic dermatitis?	**Yes:** Go to #2	**No:** Go to #3
2. Have the patient's symptoms improved with dupilumab therapy? • at least a 50% reduction in the Eczema Area and Severity Index score (EASI 50) from when treatment started OR • at least a 4-point reduction in the Dermatology Life Quality Index (DLQI) from when treatment started OR • at least a 2 point improvement on the Investigators Global Assessment (IGA) score?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the request to renew dupilumab for moderate to severe asthma?	**Yes:** Go to # 4	**No:** Go to # 6

Renewal Criteria		
4. Is the patient currently taking an inhaled corticosteroid and 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, theophylline)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Has the patient reduced their systemic corticosteroid dose by ≥50% compared to baseline?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.
6. Have the patient's symptoms of chronic rhinosinusitis with polyposis improved?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: *9/19 (DM); 7/19 (DM)*

Implementation: *TBD: 8/19/19*