INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Dupilumab for asthma***

-April/May 2024-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a drug review of dupilumab, a biologic agent approved for treatment of uncontrolled eosinophilic asthma. Medications listed on the National Core Formulary (NCF) relevant to this condition include albuterol, fluticasone/ salmeterol, mometasone, montelukast, and tiotropium. Following clinical review and analysis, the NPTC **made no changes** to the NCF.

Discussion:

Asthma affected an estimated 25 million Americans in 2020. It is characterized by expiratory air flow variability associated with chronic airway inflammation and hyper-reactivity. Symptoms include wheezing, chest tightness, cough, and breathlessness. A greater than 12% (or 200 ml) improvement in Forced Expiratory Volume in one second (FEV1) after bronchodilator use is specific for the disease.[1] In adults, its prevalence is somewhat higher in women than men. As a group, American Indians and Alaska Natives (AIAN) have the highest prevalence of the disease (12.3% vs 7.7% in the overall population), and a disease-specific mortality approximately 20% higher than average.[2]

Six biologic medications for the treatment of uncontrolled asthma have been approved by the U.S. Food and Drug Administration (FDA), beginning with omalizumab in 2003. Five have been introduced in the last nine years, including dupilumab in 2018.[3] All of these biologic medications target components of the type 2, or eosinophilic inflammatory pathway, to which 70% of severe asthma is attributed. Type 2 inflammation is associated with elevations in blood and sputum eosinophil counts, as well as in fractional exhalation of nitric oxide, measurements of which - along with other aspects of the medical history - help characterize an individual's asthma phenotype and guide therapeutic decision-making in severe or uncontrolled disease.[4] Current guidelines addressing the use of biologics in this context include the Global Initiative for Asthma Report (2023), the European Respiratory Society/ American Thoracic Society guideline for management of severe asthma (2020), and the European Association of Allergy and Clinical Immunology Biologicals Guideline in Severe Asthma (2020).

Dupilumab is a human monoclonal IgG4 antibody which binds the interleukin (IL) 4Rα subunit of IL-4 and IL-13 receptor complexes, inhibiting their downstream proinflammatory effects. It is indicated for use in patients ≥ 6 years old with moderate-to-severe uncontrolled asthma who have blood eosinophil counts ≥ 150/μL. Maintenance therapy is by subcutaneous injection given every 2 weeks after an initial loading dose.

Though industry-sponsored trials form the core evidence base for the effectiveness and safety of dupilumab, subsequent observational studies have largely corroborated their findings. A series of Phase 3 trials established its effectiveness in reducing the frequency of severe asthma exacerbations and improving pre-bronchodilator FEV1 in children > 5 years and adolescents and adults >11 years; and in allowing reduction or discontinuation of maintenance oral corticosteroids for patients > 11 years.

LIBERTY ASTHMA QUEST (2018) was a 52-week randomized placebo-controlled trial (RCT) evaluating 1902 patients ≥ 12 years with uncontrolled asthma. Primary outcomes included a lower annualized rate of severe asthma exacerbations with dupilumab 200 mg, RR 0.46 (95% CI: 0.39 to 0.53) vs. 0.87 with placebo (95% CI: 0.72 to 1.05) for OR 0.53 (p<0.001); and an average increase in pre-bronchodilator (pb) FEV1 vs. placebo of 320 ml vs 140 ml at week 12, for a difference of 140 ml (p<0.001). Outcomes were similar with a 300 mg dose. These findings did not reach significance in patients with baseline with baseline eosinophil counts <150/μL; those with counts > 300/μL had the best response rates.[5]

LIBERTY ASTHMA VENTURE (2018) was a small randomized, controlled trial (RCT) of 210 patients whose primary outcome was the percentage reduction by 24 weeks in daily oral corticosteroid (OCS) use in adolescents and adults who had been using ≥ 5 mg prednisone or prednisolone regularly during the previous 6 months. The percentage dose change was −70.1% in the dupilumab group, as compared with −41.9% in the placebo group (p<0.001); 48% vs. 25% completely discontinued their maintenance glucocorticoid.[7]

LIBERTY ASTHMA VOYAGE (2021) was 52-week trial which included 408 children aged 6-11 years with uncontrolled moderate-to-severe asthma. The annualized rate of severe asthma exacerbations was lower with dupilumab, RR 0.31 (95% CI: 0.22 to 0.42) vs. 0.75 (95% CI: 0.54 to 1.03) with placebo (RR reduction 59.3%; 95% CI: 39.5 to 72.6; p<0.001). By 52 weeks, 78% of children receiving dupilumab remained exacerbation-free compared with 60% of those receiving

placebo. Mean pb FEV1% increase from baseline was 10.5±1.0% with dupilumab and 5.3±1.4% with placebo (mean difference, 5.2%; 95% CI: 2.1 to 8.3; p<0.001).[6]

The US ADVANTAGE study, published in 2023, was an industry-sponsored retrospective study evaluating severe exacerbation rate and oral corticosteroid use in 2400 patients ≥ 12 years using a pre- and post-enrollment study design. In comparison with the 12 months prior to initiation, treatment with dupilumab was associated with a 44% reduction in severe exacerbations (IRR) 0.56, 95% CI: 0.47 to 0.57, p<0.0001) and a 48% reduction in systemic corticosteroid prescriptions (IRR 0.56, 95% CI: 0.48 to 0.56, p<0.0001).[8]

Two observational studies published in 2024 showed, despite their small sizes, statistically significant outcome improvements in patients with eosinophilic asthma after starting dupilumab, including an 80-90% reduction in asthma exacerbations; an 8% absolute improvement in predicted pb FEV1%; and a 50-70% reduction in the need for OCS.[9, 10]

There are no head-to-head trials of biologic medicines for asthma. In 2023, Pitre et al. published a network meta-analysis including 64 RCTs, among which studies of all six currently FDA approved asthma biologics were included, as well as several non-approved agents. The authors concluded that there was high certainty that dupilumab and tezepelumab reduce exacerbations and improve lung function, and moderate certainty that these two reduced hospital admissions compared with placebo. A second network meta-analysis evaluated four FDA-approved biologic agents and concluded that dupilumab was superior to benralizumab in reducing exacerbation rates, and superior to mepolizumab in improving pb FEV1.[11, 12]

In QUEST, VENTURE, and VOYAGE, adverse event rates, including serious adverse events, were similar between active treatment and placebo groups. Dupilumab was associated with a small increase in helminthic infections (primarily pinworm) in children, as well as increased rates of eosinophilia and injection site reaction in all age groups. Subsequent open-label extension studies (TRAVERSE, 2022 and EXCURSION, 2024) showed treatment-emergent adverse event rates similar to those in the parent studies. In 2023, a TRAVERSE continuation study of 393 volunteers from TRAVERSE representing a total of 432 patient-years of exposure, reported no dupilumab-related serious adverse events.

Findings:

Asthma which remains poorly controlled despite high-dose inhaled glucocorticoids with or without adjunctive OCS or other agents, is usually characterized by a Type 2 inflammatory (eosinophilic) phenotype. Dupilumab, currently the fifth of six FDA approved biologics for the treatment of eosinophilic asthma, has been shown to be effective in reducing frequency of asthma exacerbations, requirements for OCS, and in pre-bronchodilator FEV1. It appears safe though long-term patient data, particularly in children, remains limited.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

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