

## Summary

### WHAT IS ASTHMA?

Asthma is a disorder that causes the airways of the lungs to narrow or become blocked, making it difficult to breathe. Exposure to certain triggers, such as allergens, cold weather, exercise, pollution, stress, and respiratory infections, can worsen asthma symptoms. In the United States, approximately 20.4 million adults and 6.1 million children have asthma.

### TREATMENT OPTIONS

Asthma treatment depends on disease severity. Moderate to severe asthma is treated with a combination of inhaled corticosteroids and long-acting  $\beta$ 2-agonists. Additional therapies for severe asthma include muscarinic agents, leukotriene inhibitors, theophylline, and **certain biologic therapies**. ICER’s 2018 review assessed the clinical and cost-effectiveness of the following five biologics.

Biologic Therapy	FDA Indication
<b>Omalizumab (Xolair®, Genentech/Novartis)</b>	Age $\geq$ 6 years with moderate to severe persistent asthma who test positive for year-round allergens
<b>Mepolizumab (Nucala®, GlaxoSmithKline)</b>	Age $\geq$ 12 years with severe asthma and eosinophilic phenotype
<b>Reslizumab (Cinqair®, Teva)</b>	Age $\geq$ 18 years with severe asthma and eosinophilic phenotype
<b>Benralizumab (Fasenra™, AstraZeneca)</b>	Age $\geq$ 12 years with severe asthma and eosinophilic phenotype
<b>Dupilumab (Dupixent®, Sanofi/Regeneron)</b>	Age $\geq$ 12 years with moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma

### KEY REPORT FINDINGS

ICER’s report found that all five of the assessed biologics modestly reduce asthma exacerbations and improve daily quality of life, but that the treatments’ prices appear to be far out of alignment with these incremental clinical benefits. The entire therapy class would need price discounts of at least 50% to reach commonly cited thresholds for cost-effectiveness.

### KEY POLICY RECOMMENDATIONS

- To provide fair value to patients and the health system, manufacturers should lower the prices of biologic therapies for asthma so that they align with the added value they bring to patients.
- Plan sponsors should work with payers to develop insurance coverage that makes an explicit commitment to providing broad access to all new biologic treatments for asthma if manufacturers will price their products in line with independent assessments of added value to patients.
- Given that manufacturers have not yet priced these biologics at a value-based level, it is reasonable that payers offer preferential formulary status in return for lower prices, and establish prior authorization criteria to ensure prudent use.
- Specialty societies should develop a clear definition of response to biologic therapy, and the FDA should update its guidance for the assessment of outcomes in asthma therapy to standardize the patient populations studied as well as the timing and instruments used to assess outcomes.

## Clinical Analyses

### ICER EVIDENCE RATING

**How strong is the evidence that these biologic therapies improve outcomes in patients with asthma, compared to standard of care?**

	<b>Omalizumab:</b> High certainty of an incremental net health benefit
	<b>Mepolizumab:</b> High certainty of an incremental net health benefit
	<b>Reslizumab:</b> Moderate certainty of a net health benefit that is comparable or better than the standard of care
	<b>Benralizumab:</b> Moderate certainty of a net health benefit that is comparable or better than the standard of care
	<b>Dupilumab:</b> Moderate certainty of a net health benefit that is comparable or better than the standard of care

*Evidence was insufficient to distinguish between the net health benefits of these five therapies.*

### KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

**How effective are these treatments compared to standard of care?**

Asthma Exacerbations	Asthma control	Quality of life	Oral Corticosteroid Use*
 <b>Reduced</b>	 <b>Modest benefit</b> <i>Did not reach minimally important difference</i>	 <b>Modest benefit</b> <i>Did not reach minimally important difference</i>	 <b>Reduced</b>

*\*No studies of reslizumab identified for patients on chronic oral corticosteroids*

## Clinical Analyses (continued)

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### HARMS

The five drugs are well tolerated. However, injection site reactions are common and both omalizumab and reslizumab carry a black box warning for anaphylaxis.

### SOURCES OF UNCERTAINTY

- **Long-term data:** Given that many of these patients have 30- to 70-year life expectancies, there is relatively little evidence on the long-term safety and effectiveness of these treatments. Of the five treatments, only omalizumab has more than 10 years of real-world evidence.
- **Response:** There is no clear definition for a response to therapy to help guide patients and clinicians in deciding when to stop one therapy and consider switching to another.
- **Biomarkers:** There are few biomarkers that can help clinicians decide which of these drugs may be most appropriate for an individual patient.
- **Length of therapy:** Because it does not appear that these therapies result in long-term remission of asthma, the condition may worsen when treatment is stopped. The optimal length of therapy is uncertain.
- **Non-standardized assessments of quality of life:** While quality of life is an essential driver of the overall evaluation of the effectiveness of these therapies, there is no standard assessment of quality of life used across all studies.
- **Parasitic infections:** Eosinophils are part of the immune response to parasitic infections. It is unknown if therapies that decrease eosinophil counts will affect patients' ability to fight such infections.
- **Biologic comparisons:** More robust data are needed to determine how these five treatments compare to each other.

## Economic Analyses

### LONG-TERM COST-EFFECTIVENESS

#### Do the biologics meet established thresholds for long-term cost-effectiveness?

At their current prices, all five treatments **exceed commonly accepted thresholds for cost-effectiveness** of \$50,000–\$150,000 per quality-adjusted life years (QALY) gained, when compared to standard of care.

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
<b>Cost per QALY gained</b>	\$325,000/ QALY	\$344,000/ QALY	\$391,000/ QALY	\$371,000/ QALY	\$351,000/ QALY
<b>Annual net price*</b>	\$28,900	\$29,500	\$28,900	\$27,800	\$31,000

\*Average annual price of each treatment, net of discounts and rebates, as reported to ICER by each manufacturer. For a full description on how each manufacturer defines net price, see the final page of this document.

### VALUE-BASED PRICE BENCHMARKS

#### What is a fair price for the biologics based on their value to patients and the health care system?

Intervention	Current Annual List Price*	Annual Price at \$100,000 per QALY Threshold	Annual Price at \$150,000 per QALY Threshold	Discount from List Price Required to Achieve Threshold Prices	Is Current Net Price Within Value-Based Range?
<b>Omalizumab</b>	\$39,048	\$9,000	\$13,300	66% to 77%	<b>NO</b>
<b>Mepolizumab</b>	\$37,293	\$9,200	\$13,400	64% to 75%	<b>NO</b>
<b>Reslizumab</b>	\$31,637	\$6,500	\$10,400	67% to 80%	<b>NO</b>
<b>Benralizumab</b>	\$30,889	\$8,300	\$11,900	62% to 73%	<b>NO</b>
<b>Dupilumab</b>	\$38,110	\$10,100	\$14,300	62% to 73%	<b>NO</b>

\*Annual wholesale acquisition cost (WAC), prior to any discounts or rebates

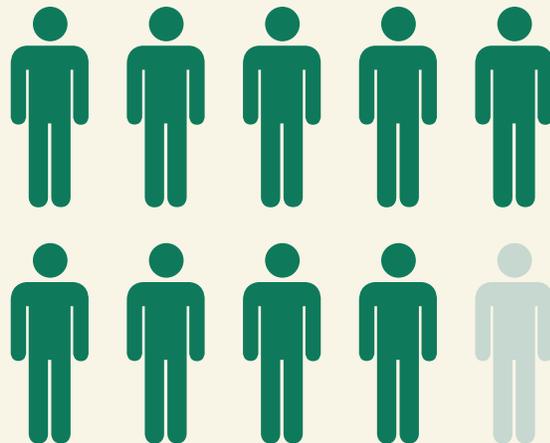
## Economic Analyses (continued)

### POTENTIAL SHORT-TERM BUDGET IMPACT

**How many patients can be treated with dupilumab, instead of standard of care or the other biologics, before crossing ICER's \$991 million budget impact threshold?**

At dupilumab's list price, **approximately 91% of the eligible population in the US could be treated each year** before the budget exceeded the ICER annual budget impact threshold of \$991 million. This budget impact reflects the incremental cost for purchasing dupilumab instead of other relevant existing therapy.

*The short-term budget impact was calculated for dupilumab only because it is the only one of these treatments that is newly approved in 2018.*



## Voting Results

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The Midwest CEPAC deliberated on key questions raised by ICER's report at a public meeting on November 29, 2018. The results of the votes are presented below. More detail on the voting results is provided in the full report.

### CLINICAL EVIDENCE

The panel found that the evidence demonstrated that dupilumab is clinically superior to the standard of care, but that the evidence was insufficient to distinguish between dupilumab and the other four biologics.

### LONG-TERM VALUE FOR MONEY

Consistent with ICER's value assessment framework, because the incremental cost-effectiveness ratios for all five biologics all exceed \$175,000 per QALY, they were each deemed "low value" without a formal vote from the panel.

### OTHER BENEFITS AND CONTEXTUAL CONSIDERATIONS

During their deliberation, panel members weighed the therapies' other benefits and contextual considerations. They acknowledged the high burden severe asthma presents to patients, and that dupilumab is intended to care for patients with a condition of high severity and a high lifetime burden of illness. They pointed out that, with a different mechanism of action from the other biologics, dupilumab may allow for the successful treatment of many patients for whom other treatments have failed, which may also lead to increased overall productivity and decreased caregiver burden.

Nevertheless, a majority of the panel felt that there is uncertainty about the long-term benefits and risks of dupilumab, citing the lack of long-term trial evidence.

## Policy Recommendations

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The Midwest CEPAC participated in a moderated policy discussion that included physicians, patient advocates, manufacturer representatives, and payer representatives. None of the resulting policy statements should be taken as a consensus view held by all participants. For a more detailed discussion, please see the full report.

### FOR MANUFACTURERS

- To provide fair value to patients and the health system, manufacturers should lower the prices of these biologic therapies so that they align with the added value they bring to patients.

### FOR SPECIALTY SOCIETIES

- Specialty societies should develop a clear definition of response to biologic therapy.
- Because of pervasive cost issues, pulmonologists, allergists and their specialty societies should advocate for prices to be better tied to the clinical benefits that drugs bring to their patients.

### FOR RESEARCHERS

- Head to head comparisons of the biologic therapies for asthma are essential.
- Better instruments to measure quality of life need to be developed.

### FOR REGULATORS

- The FDA should update its guidance for the assessment of outcomes in asthma therapy to standardize the patient populations studied as well as the timing and instruments used to assess outcomes.
- Active comparators should be the standard in pivotal trials.

### FOR PLAN SPONSORS AND PAYERS

- Plan sponsors should work with payers to develop insurance coverage that makes an explicit commitment to providing broad access to all new biologic treatments for asthma if manufacturers will price their products in line with independent assessments of added value to patients.
- In addition to step therapy, payers could reasonably develop prior authorization criteria to ensure that prescriptions are covered only for appropriate patients and that use of these expensive medications is prudent. The process for authorization of biologic therapies for asthma should be clear and efficient for providers.
- When patients change insurance, coverage for their biologic should be continued to avoid worsening of asthma control.
- Payers should not deny ongoing coverage of biologic therapy if patients are able to reduce the intensity of their long-acting controller medications during treatment with the biologic.
- Manufacturers, insurers, and governments should work to remove barriers to indication-specific pricing.

## How Each Manufacturer Defined the Net Price for These Treatments:

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**\*For omalizumab:** “Net price per 150mg vial was calculated using the manufacturer-provided annual net cost. Omalizumab’s average annual net cost per adult patient is \$28,895. Average annual net cost of treatment for adults with allergic asthma only (as of July 2018) assuming three 150 mg vials per month. Net cost assumption is an average cost reflecting all price concessions given to customers, and inclusive of all statutory discounts and rebates. This calculation is an estimate for the purposes of financial modeling. Cost of treatment per patient varies as dosing depends on age, weight and IgE level and pricing differs by provider and payer (commercial insurance or government program).”

**\*For mepolizumab:** “Average net sales price is inclusive of WAC rebates, allowances, and returns.”

**\*For reslizumab:** “This net price reflects a weighted average after applying statutory discounts.”

**\*For benralizumab:** “The net price for each 30mg/ml pre-filled syringe of Benralizumab is \$4265. This price includes government statutory rebates, allowances, and returns.” Benralizumab will have an additional cost of \$6,302.30 for the first year of treatment due to the higher frequency of administration for the first three doses.

**\*For dupilumab:** “The net price of \$31,000 should be considered as inclusive of all discounts applied to dupilumab throughout the value chain and not just reflective of rebates alone.” Dupilumab will have an additional cost of \$1,192.31 for the first year of treatment due to the loading dose.

## About ICER

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The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER’s reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER’s reports incorporate extensive input from all stakeholders and are the subject of public

hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER’s reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care. For more information about ICER, please visit ICER’s website ([www.icer-review.org](http://www.icer-review.org)).