Asthma and Allergy Foundation of America

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Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

To Whom It May Concern:

The Asthma and Allergy Foundation of America ("AAFA") along with four of its regional chapters (Maryland, Michigan, New England, and St. Louis) thank the Institute for Clinical and Economic Review ("ICER") for the Draft Report "Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation" (September 24, 2018) and the work that went into developing it.

AAFA agrees with ICER that

- **Biologic therapy costs are too high to be an option for all asthmatics with moderate to severe, uncontrolled asthma**.
- **Because of the high costs, payers restrict access to the drugs and impose cost sharing that make biologic therapies unavailable and/or unaffordable to some patients with moderate to severe, uncontrolled asthma who could benefit from the therapies**.

We appreciate that ICER is calling attention to the biologic therapy access and cost issues that impact the quality life and sometimes longevity of life of some of the more than 25 million Americans with asthma, 12 million of whom have an asthma attack during the course of a year.[1]

However, we believe that ICER understated or overlooked some important points in its analysis, specifically that

- **People with moderate to severe, uncontrolled asthma are heterogenous – some people are significantly sicker and at more risk of serious exacerbations than others and have more to gain from costly therapies.**
- **Data suggests that the number of people receiving biologic therapies is much smaller than estimated by ICER and therefore the budget impact of new therapies is smaller than estimated by ICER.**
- **Few people with asthma, if any, will receive a biologic therapy for a lifetime.**
- **It is appropriate for society to pay a premium to save a life.**
- **Real-world healthcare data, when available, should inform asthma treatment cost-effectiveness and budget impact analyses. Inputs that more accurately reflect the patients with severe asthma and the patient perspective should be included as part of ICER's base-case findings. We identify several scenarios where cost per QALY is near or below ICER's $150,000 per QALY threshold.**

Until there are new, more effective and patient-tailored asthma treatments, asthma biologic therapies are potential life-savers for some people with asthma. We are concerned that ICER's conclusions underestimate the short-term importance of asthma biologics for certain

subpopulations of patients with asthma. We suggest that ICER more extensively test the robustness of its conclusions for at-risk subpopulations.

Asthma is a Heterogenous Disease

Asthma is a cluster of respiratory-related symptoms and pathophysiology, the multiple causes of which are unclear. People with asthma, even those classified as "moderate to severe, uncontrolled" are diverse. As described by Ray and colleagues:[2]

Asthma identifies a spectrum of respiratory-related symptoms, typically with a link to reversible airflow limitation… The term asthma does not identify any specific underlying pathobiology, but is a broad, umbrella-like term that covers multiple groupings of patient characteristics or phenotypes. While the term asthma has been traditionally used to describe a childhood onset disease associated with atopic/allergic responses, asthma can develop later in life, with minimal link to allergy. Although mild to severe disease has been identified across the spectrum of asthma, many studies now show that "severe asthma" is not a phenotype, but rather a description of a group of patients with high medical needs, whose pathobiologic and clinical characteristics vary widely.

ICER calculated cost effectiveness and budget impact using estimates of the broadest possible asthma patient population for whom biologic therapies are approved: patients ages 6 and older with moderate to severe, uncontrolled asthma. Not all of the patients are good candidates for biologic therapies. Many are non-controlled because they are non-adherent on their standard-of-care (SOC) drugs and adding biologic therapies to the mix is unlikely to increase their adherence. Poor adherence, even to inexpensive SOC treatments, is an unfortunate real-world reality of asthma control.[3]

Furthermore, while biologics are broadly approved by the FDA for moderate to severe, uncontrolled asthma, payers typically impose more stringent criteria for biologic approval. The ICER Draft Report provides asthma biologic approval policies for several payers. The policies provide potential biologic approval for patients with severe (not moderate) uncontrolled asthma who have exhausted non-oral corticoid steroid options, are taking high-dose inhaled corticoid steroids (ICS), and are having regular acute asthma exacerbations or severe-persistent symptoms.

Few People Receive Biologic Therapies

Data confirms that only a minority of patients with moderate to severe, uncontrolled asthma receive biologic therapies. Xolair was approved in 2003 and to-date the singular biologic therapy approved for patients with moderate severe, uncontrolled *allergic* asthma. Novartis reports that in 2017 Xolair's worldwide net sales were $920 million.[4] If we assume that all sales were in the US (they were not) and a year of the Xolair had a net annual cost of $28,900 per patient,[5] then the total US patients per month *did not exceed* 32,000. Similarly, the FDA estimated that over the two-year period from March 2014 to February 2016, 51,000 unique US patients had a prescription or medical claim for Xolair.[6] If we assume that the average patient had claims for 12 months[7] of Xolair in the 24 month period, then there were approximately 25,000 unique patients per month. Yet the ICER Draft Report estimates that 128,500 US patients have moderate severe, uncontrolled allergic asthma (half[8] of the 257,000[9] people with

moderate to severe, uncontrolled asthma of any kind). The other approved biologic therapies are much newer[10] and are used by even fewer of the estimated 128,500 US patients with non-allergic asthma.[11]

Clearly only a subset of the patients with moderate to severe, uncontrolled asthma are receiving biologic therapies – substantially fewer than the 27% assumed in the budget impact analysis portion of the ICER Draft Report.[12] Furthermore, because payer policies purposefully restrict access to biologic therapies, there is reason to believe that the asthma patient receiving biologic therapies is sicker and more at risk of serious exacerbations than the average patient with moderate to severe, uncontrolled asthma and therefore stands more to gain from costly drugs. Such "patient selection" may significantly change ICER's cost effectiveness calculations.

Drug Patients do not Stay on One Drug or Combination of Drugs over the Long-Term

The ICER Draft Report assumes that a patient with asthma who initiates biologic therapy will continue the biologic therapy for the remainder of his/her life with 100% adherence. While we recognize that ICER's Value Assessment Framework prescribes a lifetime horizon for value assessments, we feel that a lifetime horizon is less appropriate for asthma treatments than for treatments that potentially confer a lifetime benefit (such as vaccines). We ask that ICER consider that:

- **Asthma biologic therapies are a short-term treatment that must be re-administered in 2, 4, or 8-week intervals and "it does not appear that biologic therapy results in long-term remission of asthma."[13]**
- **Payers are most concerned with this year's and next year's costs and effectiveness, not the costs or effectiveness decades from now.**
- **There is real-world evidence that with or without biologic therapies, patients with severe asthma tend to improve over time.[14] Therefore, while severe asthma is a challenging period of time for a patient, it is not a lifetime and lifelong biologic therapy will likely not be required.**
- **In the real-world, for various reasons, patients do not continue biologic therapy indefinitely. The average Medicare Part D beneficiary receiving biologic therapy received the therapy for 7 months of 2016.[15] Studies document real-world non-adherence to biologic therapy.[16]**
- **Realistically, a person with asthma who initiates biologic therapy will likely cycle between biologics and other drugs over time.**
- **We are hopeful that new, more effective and patient-tailored asthma treatments will be developed within our lifetimes. The treatments will supplement or replace today's SOC and biologic therapies**.

Life is Precious

ICER's Value Assessment Framework requires quality-adjusted life years (QALYs) as the denominator metric of cost effectiveness analyses and suggests the maximum price that society should pay per QALY gained. Like previous commenters, we are philosophically challenged with the assumption that the death of a few people can be offset by marginal quality improvements in the life of many and that there is maximum value society should be willing to pay for the prevention of death.

Asthma is a life-threatening disease, directly causing the death of 3,600 people a year[17] and contributing to deaths from other causes.[18] The people most at risk of asthma-related death will only benefit from new, more effective and patient-tailored treatments if they survive to receive those drugs.

The sub-population of people with asthma most-at-risk of death includes children with severe, uncontrolled asthma, who have particularly severe and frequent exacerbations and a lifetime of human potential to retain or lose. Yet ICER modeled cost effectiveness assuming all people with asthma are age 46 (Table 4.1)[19] and separately varied exacerbation rates and subsequent inpatient and emergency department risk of death across relatively narrow bands of risk (Table 4.18).[20]

Real-World Healthcare Data Should Inform Real-Life Drug Coverage Decisions

ICER economic assessments primarily use epidemiological data to estimate the size of the potential patient population that will benefit from the treatment of interest, randomized controlled trials (RCTs) to estimate treatment effectiveness, and real-world data to estimate treatment costs. Epidemiological data may not be up to date or definitionally aligned with the population that is a candidate for treatment and RCTs are extremely controlled and not reflective of the real-life treatment decisions and behaviors of payer, physicians, and patients. We therefore believe that, when real-world healthcare data is available, real-world healthcare data should be used to estimate the potential patient population and treatment effectiveness.

In the above discussion, we have checked the assumptions in the ICER Draft Report against readily available real-world healthcare data and noted gaps. There is, however, much more potential of real-world data to inform ICER's and other asthma treatment value assessments. Claims and enrollment data sets, such as the US data sets prepared by CMS, IBM (formerly Truven), and HCCI, are available to researchers -- often with a year or less of reporting lag. Such data sets have been underutilized for answering critical asthma disease and treatment questions. For example, it is possible to use the data to estimate the real-world reduction in asthma exacerbations for patients taking asthma biologics compared to matched patients not taking biologics.

Data collected directly from patients can also be used as patients are the experts on how asthma and other diseases impact them. For example, in calculating the societal impact of asthma, we believe ICER underestimates the days of lost work productivity. AAFA's own "My Life with Asthma" survey estimates greater than three days of lost work in the severe asthma population. Providing greater transparency into ICER's Societal Impact calculations and scenario analyses would represent true dialogue with the patient community and make ICER's analyses more relevant.

We encourage ICER to use quality real-world data, when available, as a primary data source and would applaud ICER for using its leadership to promote more real-world analyses.

We Estimate that Biologic Therapies May be Cost Effective

While we recognize that ICER attempted to test the significance of patient selection via scenario analyses, we are not convinced that the tested assumptions describe the real-world

characteristics and treatment responses of the patients with severe asthma receiving biologic treatments and potential subpopulations thereof (such as children and young adults).

The reasonable range for any given assumption may be much larger than the range that ICER tested. Furthermore, to the extent that one assumption does not fit a particular population or subpopulation, it is likely that several other assumptions also lack fit. ICER, however, tests each assumption independently – holding all other assumptions constant – and therefor underestimates the total misestimation risk.

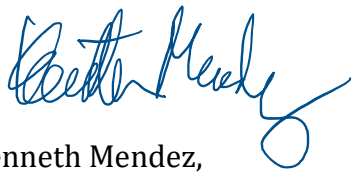
According to our estimates (see Appendices A and B), relatively modest changes in ICER's cost and utility assumptions have a significant impact on cost per QALY. For example, expanding the band of risk in SoC Utility for Non-Exacerbation (lower input) and Biologic Utility for Non-Exacerbation State (upper input) by as little as four percent brings down the associated cost effectiveness numbers (Table 4.18)[21] to ICER's target $150,000/QALY range. Similarly, a $3,210 change in the Cost for Exacerbation-Related Steroid Burst upper input brings the cost effectiveness number very close to the target $150,000/QALY range.

Likewise, simply combining a treatment responder scenario and societal perspectives, as calculated by ICER (see Appendix C) generates a best-case incremental CE Ratio range of $118,497 to $176,974; below or very close to ICER's target $150,000.

Conclusion

ICER must make sure its analyses more accurately reflect comorbidities, incremental adverse events from chronic steroid use, and the intrinsic biologic variability of the inputs associated with asthma. Greater transparency and using real-world data in ICER's modeling can make ICER's work more helpful to patients who most need these therapies. Too little is known about the multi-year natural history of asthma, the real-world use of treatments (including adherence), and the cost and efficacy of the treatments.

Sincerely,



Kenneth Mendez,
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Asthma and Allergy Foundation of America

APPENDIX A

Table 4.18: Input Name: SoC Utility for Non-Exacerbation State			
	Input Range	QALY Range	$ Change/.01 input
Lower Input	0.74	258,000	
	0.75	299,500	41,500
	0.76	341,000	41,500
	0.77	382,500	41,500
	0.78	424,000	41,500
	0.79	465,500	41,500
Upper Input	0.80	507,000	41,500

Revised QALY based on 1% Chg increments in Lower Input		
% Chg in Lower Input	Revised Lower Input	Revised $/QALY
1%	0.73	227,290
2%	0.73	196,580
3%	0.72	165,870
4%	0.71	135,160
5%	0.70	104,450
6%	0.70	73,740
7%	0.69	43,030

A four percent reduction in the lower input for SoC Utility for Non-exacerbation state reduces the $/QALY to ICER's target $150k $/QALY threshold.

Table 4.18: Biologic Utility for Non-Exacerbation State			
	Input Range	QALY Range	$ Change/.01 input
Lower Input	0.81	451,000	
	0.82	408,500	(42,500)
	0.83	366,000	(42,500)
	0.84	323,500	(42,500)
Upper Input	0.85	281,000	(42,500)

Revised QALY based on 2% Chg increments in Upper Input		
% Chg in Upper Input	Revised Upper Input	Revised $/QALY
1%	0.86	244,875
2%	0.87	208,750
3%	0.88	172,625
4%	0.88	136,500
5%	0.89	100,375

A four percent increase in the upper input for Biologic Utility for Non-exacerbation state reduces the $/QALY to ICER's target $150k $/QALY threshold.

Table 4.18: Cost for Exacerbation-Related Steroid Burst			
	Input Range	QALY Range	$ Chg/$1k input
Lower Input	$ -	355,000	
	$ 1,172	347,778	7,222
	$ 2,172	340,556	7,222
	$ 3,172	333,333	7,222
	$ 4,172	326,111	7,222
	$ 5,172	318,889	7,222
	$ 6,172	311,667	7,222
	$ 7,172	304,444	7,222
	$ 8,172	297,222	7,222
Upper Input	$ 9,172	290,000	7,222

Revised QALY based on 5% Chg increments in Upper Input		
% Chg in Upper Input	Revised Upper Input	Revised $/QALY
5%	$ 9,631	270,510
10%	$ 10,089	251,019
15%	$ 10,548	231,529
20%	$ 11,006	212,038
25%	$ 11,465	192,548
30%	$ 11,924	173,057
35%	$ 12,382	153,567
40%	$ 12,841	134,076

A $3,210 increase in the upper input for Cost for Exacerbation-Related Steroid Burst reduces the $/QALY close to ICER's target $150k $/QALY threshold.

APPENDIX B

Table 4.18: Input Name: SoC Utility for Non-Exacerbation State			
	Input Range	QALY Range	$ Change/.01 input
Lower Input	0.74	258,000	
	0.75	299,500	41,500
	0.76	341,000	41,500
	0.77	382,500	41,500
	0.78	424,000	41,500
	0.79	465,500	41,500
Upper Input	0.80	507,000	41,500

Revised QALY based on 1% Chg increments in Lower Input adding Societal Impact from Table 4.20 Mepolizumab				
% Chg in Lower Input	Revised Lower Input	Revised $/QALY	Societal Incremental QALY	QALY with Societal Impact
1%	0.73	227,290	1.63	139,442
2%	0.73	196,580	1.63	120,601
3%	0.72	165,870	1.63	101,761
4%	0.71	135,160	1.63	82,920
5%	0.70	104,450	1.63	64,080
6%	0.70	73,740	1.63	45,239
7%	0.69	43,030	1.63	26,399

A one percent reduction in the lower input for SoC Utility for Non-exacerbation state and adding societal impact reduces the $/QALY to ICER's target $150k $/QALY threshold.

Table 4.18: Biologic Utility for Non-Exacerbation State			
	Input Range	QALY Range	$ Change/.01 input
Lower Input	0.81	451,000	
	0.82	408,500	(42,500)
	0.83	366,000	(42,500)
	0.84	323,500	(42,500)
Upper Input	0.85	281,000	(42,500)

Revised QALY based on 2% Chg increments in Upper Input adding Societal Impact from Table 4.20 Mepolizumab				
% Chg in Upper Input	Revised Upper Input	Revised $/QALY	Societal Incremental QALY	QALY with Societal Impact
1%	0.86	244,875	1.63	150,230
2%	0.87	208,750	1.63	128,067
3%	0.88	172,625	1.63	105,905
4%	0.88	136,500	1.63	83,742
5%	0.89	100,375	1.63	61,580

A one percent increase in the upper input for Biologic Utility for Non-exacerbation state and adding societal impact reduces the $/QALY to ICER's target $150k $/QALY threshold.

Table 4.18: Cost for Exacerbation-Related Steroid Burst			
	Input Range	QALY Range	$ Chg/$1k input
Lower Input	$ -	355,000	
	$ 1,172	347,778	7,222
	$ 2,172	340,556	7,222
	$ 3,172	333,333	7,222
	$ 4,172	326,111	7,222
	$ 5,172	318,889	7,222
	$ 6,172	311,667	7,222
	$ 7,172	304,444	7,222
	$ 8,172	297,222	7,222
Upper Input	$ 9,172	290,000	7,222

Revised QALY based on 5% Chg increments in Upper Input adding Societal Impact from Table 4.20 Mepolizumab				
% Chg in Upper Input	Revised Upper Input	Revised $/QALY	Societal Incremental QALY	QALY with Societal Impact
5%	$ 9,631	270,510	1.63	165,957
10%	$ 10,089	251,019	1.63	153,999
15%	$ 10,548	231,529	1.63	142,042
20%	$ 11,006	212,038	1.63	130,085
25%	$ 11,465	192,548	1.63	118,127
30%	$ 11,924	173,057	2.63	65,801
35%	$ 12,382	153,567	3.63	42,305
40%	$ 12,841	134,076	4.63	28,958

A $1,376 increase in the upper input for Cost for Exacerbation-Related Steroid Burst and adding societal impact reduces the $/QALY close to ICER's target $150k $/QALY threshold.

APPENDIX C

Treatment Responder Scenario Incremental CE Ratio Cost per QALY gained including Modified Societal Perspective (vs. SoC)					
	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Treatment Responder Scenario CE Cost Ratio (Table 4.21)	$205,000	$214,000	$234,000	$222,000	$269,000
Incremental QALY from Modified Societal Perspective (Table 4.20)	1.73	1.63	1.48	1.41	1.52
Adjusted Incremental CE Ratio including societal perspective	$118,497	$131,288	$158,108	$157,447	$176,974

Adding the incremental QALY from Modified Societal Perspective to the Treatment Responder Scenario brings two of the five biologic therapies below the ICER $150,000/QALY target.

[1] CDC, Most Recent Asthma Data, retrieved October 8, 2018.
[2] Ray et al, Current concepts of severe asthma, Journal of Clinic Investigation, 2016.
[3] Engelkes et al, Medication adherence and the risk of severe asthma exacerbations: a systematic review, 2014.
[4] Novartis, Full Year 2017 Product Sales, retrieved October 8, 2018.
[5] ICER Draft Report, Table 4.17.
[6] FDA, Xolair Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review, 2016.
[7] Twelve months of therapy over 24 months is an assumption based on the fact that Medicare beneficiaries have an average of 7 months of therapy during a 12 month period (see separate citation).
[8] ICER Draft Report, pg. 2.
[9] ICER Draft Report, pg. 63.
[10] Approval dates: Mepolizumab, 11/2015; Reslizumab, 3/2016; Benralizumab, 11/2017.
[11] ICER Draft Report, pg. 64.
[12] ICER Draft Report, pg. 64.
[13] ICER Draft Report, pg. 29.
[14] Chen et al, The natural history of severe asthma and influences of early risk factors: a population-based cohort study, 2016.
[15] CMS, PartD_Prescriber_PUF_Drug_Ntl_16.xlxs, retrieved October 8, 2018.
[16] Caminati et al, Drop-out rate among patients treated with omalizumab for severe asthma: Literature review and real-life experience, 2016.
[17] CDC, Most Recent Asthma Data, retrieved October 8, 2018.
[18] To et al, Asthma Deaths in a Large Provincial Health System. A 10-Year Population-Based Study, 2014.
[19] ICER Draft Report, pg. 35.
[20] ICER Draft Report, pg. 51.
[21] ICER Draft Report, pg. 51.