CALIFORNIA TECHNOLOGY ASSESSMENT FORUM℠

Mepolizumab (Nucala®, GlaxoSmithKline plc.) for the Treatment of Severe Asthma with Eosinophilia

February 12, 2016

1

CTAF Overview

- Core program of the Institute for Clinical and Economic Review (ICER)
- Goal: Help patients, clinicians, insurers, and policymakers understand and apply evidence to improve the quality and value of health care
- Deliberation and voting by CTAF Panel – independent clinicians, methodologists, and public representatives
- Supported by grants from the Blue Shield of California Foundation, the California HealthCare Foundation, and the Laura and John Arnold Foundation

2

Agenda

- **Public Meeting Convened, Topic Overview** | 12:40 pm
- **Presentation of the Evidence and Economic Modeling, Q&A** | 12:45 – 1:30 pm (Dr. Jeff Tice, Melanie Whittington, and Dr. Dan Ollendorf)
- **Public Comments** | 1:30 – 2:00 pm
- **CTAF Deliberation and Votes** | 2:00 – 2:30 pm
- **Policy Roundtable Discussion** | 2:30 – 3:20 pm
- **Reflections from CTAF Panel** | 3:20 – 3:30 pm
- **Summary, Closing Remarks** | 3:30 pm
  - **Download meeting materials:** http://tinyurl.com/ctaf-mepo

3

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Evidence Review

Jeffrey A. Tice, MD
Division of General Internal Medicine
University of California, San Francisco

4

Disclosures:

I have no conflicts of interest

Key review team members:

Dan Ollendorf, PhD
Jed Weissberg, MD
Shanshan Liu, MS, MPH
Elizabeth Russo, MD

5

Topic in Context

- Asthma: 22 million Americans
- Severe asthma
  - Daily symptoms limiting normal activities; 2+ exacerbations requiring oral corticosteroids (OCS) in past year
  - 5-10% of asthma but 50% of costs
  - Standard treatment: inhaled corticosteroids (ICS) plus long acting beta agonist (LABA)
  - Additional therapies: leukotriene inhibitors, theophylline, and omalizumab
- OCS used for asthma exacerbations and chronically for severe asthma not controlled without OCS
  - Chronic OCS associated with many long-term **complications**: infections, diabetes, osteoporosis, myopathy, obesity, glaucoma, depression, delirium, hypertension, adrenal suppression, cataracts, etc.

6

Mepolizumab

- Humanized monoclonal antibody to IL-5
  - Binds to IL-5, decreasing IL-5 signaling, leading to decreased eosinophils in blood and tissue
- FDA-approved November 2015
  - Mepolizumab 100 mg SC every 4 weeks in MD office
  - Requires reconstitution by office staff
  - Indication: Patients ≥ 12 years old with severe eosinophilic asthma
    - Blood eosinophils ≥ 150 cell/μL at initiation or eosinophils ≥ 300 cell/μL in prior year

7

Methods

- Systematic review following PRISMA guidelines
- Target population (FDA indication):
  - Adults and children ages 12 years and older with severe, uncontrolled asthma and evidence of eosinophilic inflammation
- Intervention
  - Mepolizumab 100 mg SC (primary)
  - Mepolizumab 75 mg IV (similar pharmacodynamics)
- *Comparator:*
  - Standard treatment for severe asthma (OCS added to daily ICS and other controller therapy alone)

8

Double-blind RCTs

- MENSA trial (**100 mg SC** or 75 mg IV vs. placebo):
  - 576 patients age 12+ years and at least 2 asthma exacerbations in past year
  - 24 week F/U
- SIRIUS trial (**100 mg SC** vs. placebo):
  - 135 patients age 12+ years requiring 5-35 mg of prednisone daily for at least 6 months
  - 36 week F/U
- DREAM trial (**75** or 250 or 750 mg **IV** q 4 weeks):
  - 616 patients age 12+ years and at least 2 asthma exacerbations in past year
  - 52 week F/U

9

Annual Exacerbation Rates

	N	Baseline	End	Rate Ratio
MENSA				
100 SC	194	3.8	0.8	0.5 (0.4-0.6)
75 IV	191	3.5	0.9	0.5 (0.4-0.7)
Placebo	191	3.6	1.7	
SIRIUS				
100 SC	69	3.3	1.4	0.7 (0.5-1.0)
Placebo	66	2.9	2.1	
DREAM				
75 IV	153	3.7	1.2	0.5 (0.4-0.7)
Placebo	155	3.7	2.4	

10

Oral Corticosteroid Use (mg/day)

Median dose

	N	Baseline	End	Difference
SIRIUS				
100 SC	69	10.0	3.1	6.9
Placebo	66	12.5	10.0	2.5

Mean dose

	N	Baseline	End	Difference
SIRIUS				
100 SC	69	12.4	8.6	3.8
Placebo	66	13.2	10.5	2.7

Median dose reduction: 50% versus 0%, P=0.007

11

Quality of Life

- Statistically significant modest improvements
  - Asthma Control Questionnaire
  - St. George's Respiratory Questionnaire

12

Adverse Events

- Injection site reactions 8% versus 3%
- No difference in SAEs
- No difference in hypersensitivity reactions
- Opportunistic infections
  - Patients with parasitic infections excluded
  - Nominally more herpes zoster infections
    - 2/263 versus 0/257

13

Effectiveness: Controversies and Uncertainties

- Relatively small number of patients treated with SC
  - MENSA: 194 participants
  - SIRIUS: 69 participants
- Short duration of follow-up
  - MENSA: 32 weeks
  - SIRIUS: 24 weeks
- Key subgroups too small to evaluate
  - African descent: n = 39
  - Ages 12 to 17 years: n = 27

14

Effectiveness: Summary

- Moderate certainty of comparable or better net benefit for mepolizumab as add-on maintenance treatment compared with standard of care
- Other benefits or disadvantages:
  - Potential reduction in long-term harms associated with chronic OCS use
  - Injection that requires office visit every four weeks creates travel burden and may decrease long-term adherence
    - Conversely, monitoring and opportunity for patient education may offer additional benefits
  - New mechanism of action to treat severe asthma

15

Public Comments Received

- Mepolizumab 75 mg IV data should be included as it has equivalent pharmacodynamics
- Unpublished, ongoing open label continuation studies of the published trials provide data on the durability of the benefits
- Potential long term benefits through effects on airway remodeling may lead to greater benefits with mepolizumab treatment
- The large placebo effect on exacerbation rates suggests that optimization of standard therapy alone may greatly improve outcomes

16

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Incremental Costs per Outcomes Achieved

Jon Campbell, PhD & Melanie Whittington, MS
Department of Clinical Pharmacy
Center for Pharmaceutical Outcomes Research
University of Colorado Anschutz Medical Campus

17

Disclosures:

Financial support provided to the University of Colorado from the Institute for Clinical and Economic Review (ICER).

Key review team members:

Rick Chapman, PhD, MS
Jeff Tice, MD
Dan Ollendorf, PhD

18

Research Question

What are the outcomes, costs, and cost-effectiveness of mepolizumab plus standard of care (SoC) compared with SoC alone?

19

Methods

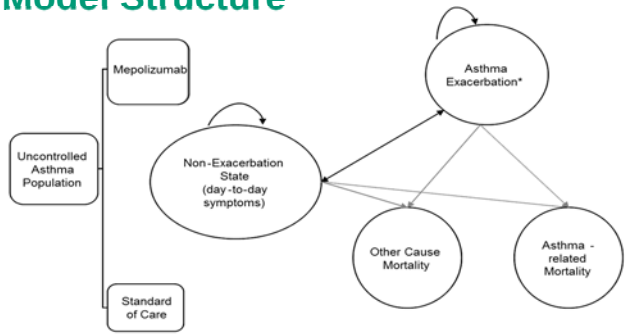
- Population: adults with severe, uncontrolled asthma and evidence of eosinophilic inflammation

	Value	Source
Mean age	50	Ortega et al., 2014
Female	57%	Ortega et al., 2014
Caucasian	90%	Ortega et al., 2014
Mean FEV_1 % of predicted	61%	Ortega et al., 2014
Mean reversibility	28	Ortega et al., 2014
Mean blood eosinophil	445	Ortega et al., 2014

- Payer perspective: direct medical care and drug costs
- Time Horizon: lifetime

20

Model Structure



Exacerbation is defined as one of three subcategories:

1. Asthma related event that requires an oral steroid burst of at least three days (but not ED visit or hospitalization)
2. Asthma related event that requires ED visit (but not a hospitalization)
3. Asthma related event that requires a hospitalization

Key Assumptions

- Treatment effect observed during the trials is consistent throughout the model time horizon
- Excess risk of death from exacerbation assumed only for hospitalized cases
- Oral corticosteroid use above 5mg/day is potentially harmful to the patient
- Exacerbation utility is the same across treatment strategies
- Non-exacerbation utilities are different across treatment strategies based on SGRQ mapping

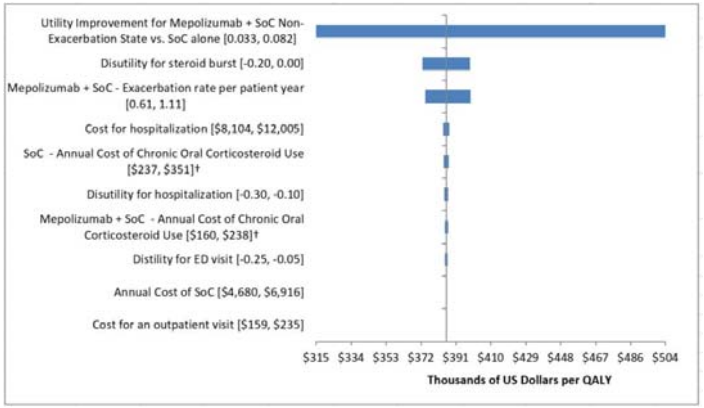
Results: Base Case

Mepolizumab + SoC vs. SoC Alone

	QALYs	Treatment Costs	Non-Treatment Costs	ICER ($/QALY)
Mepolizumab + SoC	15.12	$706,111	$15,465	
SoC alone	13.59	$98,083	$33,552	
Incremental	1.53	$608,028	-$18,087	$385,546/QALY

Treatment costs include the cost of mepolizumab and SoC. Non-treatment costs include the cost of exacerbations and chronic OCS use.

Results: One-way Sensitivity Analysis



† This value is a function of three inputs: (1) Annual cost of chronic oral corticosteroid use, (2) Annual cost of adverse events due to chronic oral corticosteroid use, (3) Treatment-specific percent using chronic oral corticosteroids >5mg per day.

Results: Scenario Analysis

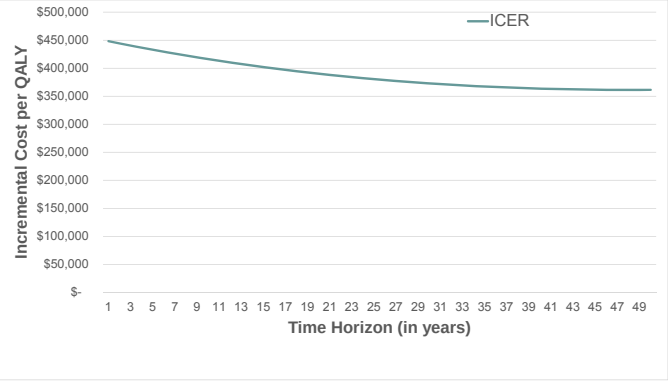
Cost of Mepolizumab

ICER	Price per Vial (discount from base-case)	Price per Year
$50,000/QALY	$266 (89.4%)	$3,458
$100,000/QALY	$599 (76.0%)	$7,787
$150,000/QALY	$932 (62.7%)	$12,116
$385,546/QALY	$2,500	$32,500

25

Results: Scenario Analysis

Length of Time Horizon



26

Key Model Limitations

- Limited long-term follow-up data
- Clinical outcomes and benefits observed in trial may not be constant through time
- Lack of absenteeism data to account for productivity differences from a societal perspective
- Responder scenario and comparison with omalizumab not conducted
- Wholesale acquisition cost of drugs may not represent true transaction cost of drugs

27

Conclusions

- Adding mepolizumab to SoC for adult patients with severe eosinophilic asthma appears to confer clinical benefits in terms of reduced rates of exacerbation and improved quality of life
- However, the estimated cost-effectiveness of mepolizumab exceeds commonly-cited thresholds
- Achieving levels of value more closely aligned with patient benefit would require discounts of two-thirds to three-quarters from current list price of mepolizumab

28

Public Comments Received

- Omalizumab (Xolair) was not modeled as a comparator
- Thresholds of $50,000 to $150,000/QALY are too low when assessing primarily employed populations
- More clarity needed on how trial data was extrapolated to assume lifetime clinical effects
- Payer perspective does not account for substantial out-of-pocket costs incurred by patients on multiple medications

29

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Potential Budgetary Impact

Daniel A. Ollendorf, PhD
Chief Scientific Officer
Institute for Clinical and Economic Review

30

Disclosures:

I have no conflicts of interest.

Key review team members:

Rick Chapman, PhD, MS

31

Budget Impact: Methods

- Estimated # of patients age 12 and older with severe asthma with poorly controlled disease (defined as 2+ exacerbations in prior year) and eosinophilic inflammation (150+ cells/μl at treatment initiation):
  - ~320,000
- Assumed uptake: 10% by year 5
- Year 5 treated estimate: 32,035

32

Annual Budget Impact Threshold: Methods

- Based on calculations involving:
  - Target for overall health care cost growth (GDP+1%)
  - Number of new drug approvals annually
  - Contribution of drug spending to overall health care spending
- Serves as “policy trigger” for discussion of managing cost of new interventions
- 2015-2016 threshold is $904 million for drugs

33

Budget Impact: Results at 5 Years

Treatment	Eligible Population (thousands)	Number Treated (thousands)	Weighted BI per Patient ($)*	Average BI per year (millions)
Mepolizumab	320	32.0	$93,043	$596.1

34

Public Comments Received

- No comments received on budget impact analysis

35

SUPPLEMENTAL SLIDES

36

Model-wide Inputs	Value	Sources
Asthma-related mortality per 100 person years	0.4	de Vries et al. 2010
Additional risk of death given asthma hospitalization	2.48%	Watson et al., 2007
Additional risk of death given ED visit	0%	Assumed
Additional risk of death given oral corticosteroid burst	0%	Assumed
Disutility for hospitalization	-0.2	Lloyd et al., 2007
Disutility for ED visit	-0.15	Lloyd et al., 2007
Disutility for oral corticosteroid burst	-0.10	Lloyd et al., 2007
Disutility for chronic oral corticosteroid use	-0.023	NICE omalizumab manufacturer's base-case, 2013
Cost for asthma-related hospital stay	$9,960	Cangelosi et al., 2015
Cost for asthma-related ED visit	$684	Cangelosi et al., 2015
Cost for oral corticosteroid burst exacerbation	$156	Cangelosi et al., 2015 & Redbook®
Annual cost for Standard of Care	$5,738	Cangelosi et al., 2015 & Redbook®
Annual cost of chronic oral corticosteroid use	$73	Redbook®
Annual cost of adverse events due to chronic oral corticosteroid use	$784	Shah et al., 2013

Treatment-Specific Model Inputs	Value	Source
SoC		
Annual exacerbation rate per person year	1.74	Ortega et al., 2014
Proportion of hospitalizations	5.75%	Ortega et al., 2014
Proportion of ED visits	5.75%	Ortega et al., 2014
Proportion of oral corticosteroid bursts	88.51%	Ortega et al., 2014
Discontinuation rate over entire time horizon	6%	Ortega et al., 2014
Utility value for non-exacerbation health state	0.77	Ortega et al., 2014
Percent using chronic oral corticosteroids >5mg per day	68%	Bel et al., 2014
Mepolizumab + SoC (limited to parameters that differ from SoC alone)		
Annual exacerbation rate per person year	0.83	Ortega et al., 2014
Proportion of hospitalizations	3.61%	Ortega et al., 2014
Proportion of ED visits	6.02%	Ortega et al., 2014
Proportion of oral corticosteroid bursts	90.36%	Ortega et al., 2014
Annual cost for mepolizumab	$32,500	Redbook®
Discontinuation rate over entire time horizon	5%	Ortega et al., 2014
Utility value for non-exacerbation health state	0.828	Ortega et al., 2014
Difference in utility value for non-exacerbation health state (compared to SoC alone)	0.059	Ortega et al., 2014
Percent using chronic oral corticosteroids	46%	Bel et al., 2014

38

Public Comments

39

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Questions for Deliberation

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Comparative *Clinical Effectiveness* Example Question

For patients with "**condition X,**" is the evidence "**adequate**" to demonstrate that the net health benefits of "**intervention A**" is greater than that of "**comparator B**"?

Yes

No

41

Care Value Example Question

Given the available evidence, what is the care value of "**intervention A**" vs. "**comparator B**"?

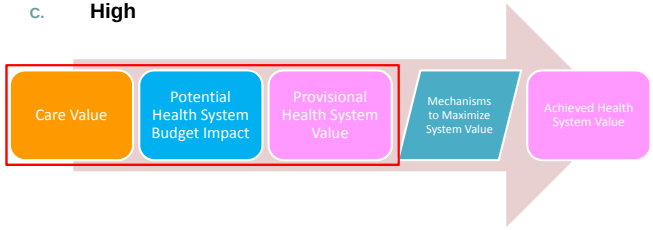
A. **Low**
B. **Intermediate**
C. **High**

42

Provisional Health System Value Example Question

Given the available evidence, what is the **provisional health system value** of "**intervention A**" vs. "**comparator B**"?

A. **Low**
B. **Intermediate**
C. **High**



43

Mepolizumab: Clinical Effectiveness

Q1. For patients with severe asthma and with an eosinophilic phenotype, is the evidence adequate to demonstrate that the net health benefit of adding ***mepolizumab to standard of care*** is greater than that of ***standard of care alone***?

Yes

No

44

Mepolizumab: Care Value

Q2. Given the available evidence for patients with severe asthma and with an eosinophilic phenotype, what is the care value of adding ***mepolizumab to standard of care*** vs. ***standard of care alone***?

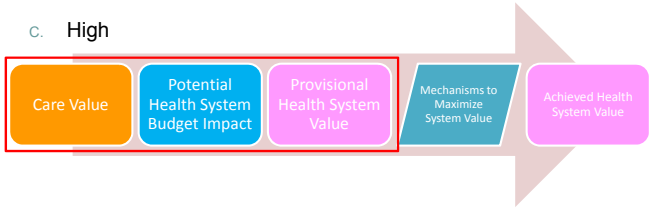
A. Low
B. Intermediate
C. High

45

Mepolizumab: Provisional Health System Value

Q3. Given the available evidence for patients with severe asthma and with an eosinophilic phenotype, what is the provisional health system value of adding ***mepolizumab to standard of care*** vs. ***standard of care alone***?

A. Low
B. Intermediate
C. High



46

Policy Roundtable Participants

- **Neal Kohatsu, MD, MPH**, Medical Director, California Department of Health Care Services
- **Michael Peters, MD, MAS**, Assistant Professor, UCSF Division of Pulmonary and Critical Care Medicine and Pulmonologist, UCSF Severe Asthma Clinic
- **Kristina Philpott, MD**, Chair, Allergy and Immunology Department, Palo Alto Foundation Medical Group
- **Tony Van Goor, MD, MMM, CPE, FACP,** Senior Director, Medical Affairs, Medical Director for Policy and Technology Assessment, Blue Shield of California
- **Tonya Winders, MBA**, President and CEO, Allergy & Asthma Network

47

Reflections from CTAF Panel

48

Summary and Closing Remarks

49

Meeting Adjourned

50