Public Comments Received on "Mepolizumab (Nucala, GlaxoSmithKline plc.) for the Treatment of Severe Asthma with Eosinphilia" By January 12, 2016

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To: California Technology Assessment Forum (CTAF), by email to ctaf@icer-review.org

From: Richard KP Sun, MD, MPH, Sacramento, CA (as an individual, not as a representative of any organization)

Date: December 30, 2015

Subject: **Recommendations Concerning "Mepolizumab (Nucala®, GlaxoSmithKline plc.) for the Treatment of Severe Asthma with Eosinophilia: Effectiveness, Value, and Value-Based Price Benchmarks | Draft Report | December 21, 2015"** (accessed December 27, 2015 at http://ctaf.org/sites/default/files/u148/Asthma_Draft_Report_122115.pdf)

Thanks to CTAF for another splendid draft report. The recommendations below are separated into "Content" ("C") versus "Formatting and Other Relatively Minor Issues" ("F"). Please note that since the CTAF insulin degludec and mepolizumab draft reports released the same day share many features, many of the recommendations concerning the two reports are similar or identical.

CONTENT

Recommendation C1: In the title, make the part after the colon "Effectiveness, Value, and Related Considerations."

The discussion of value-based price benchmarks is only a small part of the report and can be subsumed under the rubric of "Value." The report contains information that cannot be classified as either "Effectiveness" or "Value" (see Recommendations C4 and F4 below).

Recommendation C2: Shorten the executive summary.

Although there is no universally-accepted standard, many Web pages at .edu domains suggest that the length of such a summary not exceed 10% of the length of a full report.[1] In a separate email please find edits to bring the executive summary of the 59-page mepolizumab full report (prior to any changes recommended below) down to about 5 pages.

Recommendation C3: Add relevant references.

The PICOTS framework on page 1 needs a reference. Appendix D, "Previous Systematic Reviews and Technology Assessments," lacks Powell C, et al. Mepolizumab versus placebo for asthma. Cochrane Database Syst Rev. 2015 Jul 27;7:CD010834.

Recommendation C4: Combine "3. Summary of Coverage Policies" and "Appendix C. Public and Representative Private Insurer Coverage Policies" to become an Appendix after "Comparative Value Supplemental Information."

Material on coverage policies was absent from CTAF reports before "Supplemental Screening Tests Following Negative Mammography in Women with Dense Breast Tissue" of late 2013. Such material does not directly pertain to the two pillars of current reports, which are "Effectiveness" and "Value" (Recommendation C1 above). Based on documents at the CTAF Web site, information on coverage policies is used only in the Policy Roundtable (after CTAF votes on effectiveness and value are counted) and in Action Guides. Other parts of the draft document (e.g., the Executive Summary) do not refer to the coverage policies section. Unlike

published scientific literature, coverage policies change frequently. The CTAF Panel excludes "current employees of any California state health agency [or] private insurer,"[2] which is inconsistent with discussion of coverage policies in a background document for the CTAF Panel. Technology assessments and related documents produced by organizations such as AHRQ and USPSTF do not consider coverage policies by insurers.

Recommendation C5: Delete Appendix Table A1, "PRISMA 2009 Checklist," and the reference to Appendix Table A1 under "4. Comparative Clinical Effectiveness."

The PRISMA list is readily available on the Web, pertains more to reporting of methods rather than the preferred methods themselves, is not specific to CTAF, and contains steps other than "Search Strategies and Results" (the title of Appendix A).

Recommendation C6: Under "6. Comparative Value," re-do the tornado diagram.

On page 27 it seems unlikely that all the bars are left-right symmetrical around a value of approximately $384,000 per QALY. Compare with the asymmetric bars on the right sides of Figures 5A and 5B in the insulin degludec report.

Recommendation C7: Under "6.4 Potential Budget Impact," revise Figure 6 ("Combined Cost-effectiveness and Potential Budget Impact") and the accompanying text.

On page 33, the "As can be seen in Figure 6..." text confuses the reader. The word "national" should be used to indicate that the "annual budget impact" is not California-specific. The title of Figure 6 does not describe the data well. There does not seem to be a reason for the blue and green colors of two graph lines. The best estimate of uptake (10%) should be indicated as a vertical bar and the $904M threshold as a colored horizontal bar. It is unreasonable to show budget impact for uptake that is over two times the best estimate (i.e., uptake that is >20%). Please see the separate email displaying specific recommended edits to the text and figure.

Recommendation C8: Request that the CTAF Panel and Advisory Board formally vote to adopt or reject the methodologies underlying "6.4 Potential Budget Impact" and "6.5 Draft Value-based Benchmark Prices," especially the concept of "Potential Budget Impact Threshold."

Beyond the brief explanation in section 6.4, "Potential Budget Impact," I cannot find detailed information on how the total national $904 million "Potential Budget Impact Threshold" was decided upon.[3] At CTAF, the concept appears to have been introduced with the CardioMEMS and Entresto draft paper of September 2015.[4] Although there do not seem to be any public comments on the "Potential Budget Impact Threshold" on the CTAF site, public comments for the New England CEPAC's draft paper on PCSK9 inhibitors earlier this year expressed concerns with the concept[5] that in my opinion were incompletely addressed[6].

While the threshold is appealing because it takes into consideration both the utilization of a drug and its per-unit cost, it is problematic because it does not account for variation across health plans. Let us consider hypothetical drugs X and Y. Drug X costs $100 per patient per year and will be used by 5M Americans, for a total national expenditure of $500M. Drug Y costs $1M per patient per year and will be used by 500 Americans, for a total national expenditure of $500M. Neither drug will exceed the national "Potential Budget Impact Threshold"; however, the impact

of Drug Y on a single health plan can be considerable, making it worthy of "policy actions to manage affordability."

CTAF might want to add a separate "Individual Cost Impact Threshold" of $12,502 per patient per year, which is double the 2015 average annual premium for employer-based health coverage for a single person.[7] At current list prices, mepolizumab for an individual patient will exceed $12,502 per year, making it a high-priority subject for potential policy actions even if it will not meet the national "Potential Budget Impact Threshold" until uptake reaches about 15%.

More broadly, the methodologies underlying "6.4 Potential Budget Impact" and "6.5 Draft Value-based Benchmark Prices" appear unique to the Institute for Clinical and Economic Review and to my knowledge have not been published in a peer-reviewed scientific journal. (In contrast, the methods used for sections 4.1-4.3 on Comparative Clinical Effectiveness and for sections 6.1-6.3 on Comparative Value are widespread in the academic literature.) It is therefore important that CTAF formally accept the 6.4/6.5 methodology prior to issuing reports using the methodology. Currently, there is nothing on the CTAF Web site suggesting that the CTAF Panel and Advisory Board have thoroughly contemplated the pros and cons of the approaches embodied in 6.4 and 6.5.

FORMATTING AND OTHER RELATIVELY MINOR ISSUES

Recommendation F1: Create a file naming convention that includes the specific service being studied and the term "CTAF." Such a convention would help people who download a file to find it later on their computers. A file name such as "Mepolizumab_Draft_Report_CTAF122115" would have been better.

Recommendation F2: Place a unique identifier in the footer of each page with the date, the nature of the document (eg, draft vs final), the term "CTAF," and the specific service being studied. One possibility would be to place in the footer the improved file name per Recommendation F1.

Recommendation F3: In four places (starting with "3. Summary of Coverage Policies"), correct the punctuation/capitalization of "CVS Caremark" to "CVS/caremark."[8]

Recommendation F4: Move section 5, "Other Benefits or Disadvantages," to an Appendix. This information is not pertinent to either "Effectiveness" or "Value" (see Recommendation C1 above).

Recommendation F5: In Appendix E, change the title to "Ongoing Registered Clinical Trials" and add ClinicalTrials.gov as a source. "Ongoing Studies" is too general a title if the list includes only clinical trials registered at ClinicalTrials.gov.

Recommendation F6: Improve the tables in Appendix F (e.g., by increasing font size and by deleting unnecessary gridlines). Due to space limitations here, for details please see the attachment to the separate email.

REFERENCES

1. For example, see http://libguides.usc.edu/writingguide/executivesummary , https://www.uakron.edu/cba/docs/communications/WritingExecutiveSummaries.pdf , http://classes.engr.oregonstate.edu/mime/fall2011/ie497/Handouts/executive_summary.pdf , https://www.umuc.edu/writingcenter/writingresources/exec_summaries.cfm , http://writing.colostate.edu/guides/guide.cfm?guideid=76 , http://public.wsu.edu/~campbelld/engl402/execsum.htm , http://facpub.stjohns.edu/~flanagap/3305/readings/executive_summary.doc , and https://www.isenberg.umass.edu/sites/default/files/Documents/Executive_Summaries.pdf . Indeed, some Web pages at .edu domains, such as http://www.muskingum.edu/dept/polisci/downloads/WritinganExecutiveSummary.pdf and http://www.newhaven.edu/772778.pdf , advise capping an executive summary at 5% of the number of pages in a full report.
2. http://ctaf.org/about-ctaf/news/2012/panel-application-process
3. The documents linked to http://www.icer-review.org/impact-and-%20outcomes/value-assessment-project/ contain some background information, but there does not appear to be a full white paper about the threshold.
4. http://ctaf.org/sites/default/files/u148/CHF_Draft_Report_091115.pdf
5. At http://cepac.icer-review.org/wp-content/uploads/2015/04/Public-Comments-PCSK9.pdf , one sees criticisms such as "The ICER warning threshold for a drug's budget impact is not a meaningful method for assessing health system value" (PDF page 9); "ICER's model applies the same $900 million threshold for all new medicines regardless of the size of the population being treated by the medicine, and is not linked to the clinical importance or effect size of the particular medicine" (page 10); "The approach outlined by ICER sets a budget threshold of $904 million in total annual costs for a new drug. Applying this threshold to past innovations, such as statins and anti-retrovirals, would have limited access to these drugs at the time they were introduced to the market" (page 19).
6. At http://cepac.icer-review.org/wp-content/uploads/2015/04/PCSK9_-PublicComment_ResponseSummary_100815.pdf , the only response was "The annual budget threshold of $904 million was also criticized as an arbitrary 'cap' that is exclusively focused on drug cost and not on the net clinical benefit to patients. As described in the report, this threshold is intended to serve as a policy trigger to stimulate efforts to address utilization, pricing, and payment mechanisms to improve overall health system value."
7. Claxton G, Rae M, Panchal N, Whitmore H, Damico A, Kenward K, Long M. Health benefits in 2015: stable trends in the employer market. Health Aff (Millwood). 2015 Oct 1;34(10):1779-88. doi: 10.1377/hlthaff.2015.0885.
8. e.g., see "CVS Caremark Announces Corporate Name Change to CVS Health to Reflect Broader Health Care Commitment" at https://www.cvshealth.com/content/cvs-caremark-announces-corporate-name-change-cvs-health-reflect-broader-health-care and current web site at https://www.caremark.com .

January 12, 2016

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Dear Mr. Seidner:

We provide recommended revisions to the Draft Report on mepolizumab (NUCALA®) based on published literature, presentations at scientific conferences and internal data on file. The evidence of net benefit has been demonstrated through the 3 well-controlled clinical trials (DREAM[1], MENSA[2], and SIRIUS[3]) and long-term effectiveness without loss of treatment benefit has been demonstrated in 2 open-label studies[4,5]. We believe this evidence should result in a clinical judgment greater than *"moderate certainty of a comparable or better net clinical benefit compared to standard of care (SOC)."* In addition, we believe that suggested clarification on the cost-effectiveness and budget impact models would provide the CTAF panel with greater insights on the burden of refractory severe asthma with eosinophil phenotype and the benefit of NUCALA.

Comparative Clinical Effectiveness

Certainty of Results: Inclusion of DREAM and MENSA trials (75mg IV arm) in consideration of NUCALA efficacy

GSK recognizes that ICER prefers to avoid use of efficacy data in which the tested agent was dosed via an unapproved route. However, mepolizumab acts systemically and the IV dose (75 mg) has been demonstrated to be pharmacodynamically equivalent to NUCALA 100 mg SC.[6,7] The dose rationale supporting 100 mg SC for patients with severe asthma with an eosinophilic phenotype is based on an integrated evaluation of the systemic exposure of IV and SC mepolizumab, the associated pharmacodynamic responses on blood eosinophils, and the associated clinical efficacy responses. (See Figure 1)

Comparability of results between 75 mg IV and 100 mg SC mepolizumab is also supported by the FDA (FDA Ad Com Briefing Document[8] [page 8, Dose Selection]) which stated:

> *"Importantly, similar treatment effects were seen in Study 88* [MENSA] *providing evidence that the data from the 75 mg IV dose can be applied to the 100 mg SC dose. The data from these three studies support the conclusion that mepolizumab 75 mg IV and 100 mg SC would provide similar efficacy."*

Therefore, we believe that the scientific evidence supports the inclusion of the 75 mg IV treatment arms from both DREAM[1] and MENSA[2] in the clinical assessment of NUCALA.

Certainty of Results: Inclusion of open-label studies with data on duration of effect

Given the positive results of the clinical trial programs and the substantial morbidity of the disorder, it was decided that it was ethically difficult to justify longer periods of study with placebo treatment arms. Therefore, 2 open-label extension trials were designed to gain additional long-term safety and efficacy data.[4,5]

COLUMBA (MEA115666), was initiated for subjects (n=347) formerly treated in DREAM and is currently ongoing (anticipated completion April 2018).[4] COSMOS (MEA115661) enrolled subjects (n=651) from both MENSA and SIRIUS and is complete.[5] All subjects in the open-label trials are/were receiving NUCALA 100 mg SC every 4 weeks for approximately 3.5 years (COLUMBA) and up to 52 weeks (COSMOS) regardless of treatment assignment in the parent study. COLUMBA data are not presented as this study is ongoing.

1. COSMOS[5]
    - Exacerbations: by Week 52, 48% of subjects experienced on-treatment exacerbations, 9% of subjects experienced exacerbations requiring hospitalization or an ED visit and 6% of subjects experienced exacerbations requiring hospitalization. The annualized rate of exacerbations was 0.93 which was consistent with results seen in the active treatment arms of the clinical trials.
    - Durability of steroid reduction obtained in SIRIUS: In the SIRIUS study, patients on mepolizumab reduced their OCS dose to a median of 3.1 mg per day.[3] The median dose of OCS remained low at 2.5 mg per day in these patients in the COSMOS trial confirming the long-term durability of OCS reduction.
    - Asthma control: Subjects previously treated with placebo in MENSA and SIRIUS showed decreases (improvement) from baseline in ACQ-5 scores (-0.3 points). In subjects previously treated with mepolizumab, improvements achieved within the double-blind studies were sustained.
    - The incidence of SAEs: was similar to those observed in the placebo-controlled clinical trials (DREAM, MENSA and SIRIUS).

Comparative Value

Clarity of Approach: Deviation from scoping document with respect to inclusion of omalizumab (XOLAIR) in the assessment

Omalizumab is an FDA-approved biologic agent used to treat moderate to severe persistent asthma, specifically in patients (12 years of age and above) with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids.[9] Omalizumab is recommended by international consensus-based guidelines (NHLBI 2007[10], GINA 2015[11]); and, should be considered as part of standard of care for severe persistent asthma. Using the US prescribing information for omalizumab, approximately 30% of the subjects in the MENSA study had elevated IgE levels and could have been eligible for treatment with omalizumab[12]; thus, supporting the notion that physicians and patients will have a choice between initiating either agent within this overlap population. ICER's Scoping Document acknowledges omalizumab as part of standard care for severe persistent asthma and that the product would be included in the assessment; yet, it has not been included in the modeling exercise.

GSK notes that exclusion of omalizumab is a significant limitation of the assessment and counter to published best practices for modeling that recommend consideration of 'all practical interventions'[13]. GSK acknowledges the challenges with respect to data for assessment, especially as it relates to comparisons between NUCALA and omalizumab. However, data are now available that would inform inclusion of omalizumab in the assessment, including an indirect treatment comparison between NUCALA and omalizumab[14,15] and an epidemiologic study to assess the potential overlap in NUCALA and omalizumab populations[16].

Finally, GSK believes that comparisons between the results of the ICER NUCALA model and the earlier omalizumab model[17] may mislead the audience as to the clinical, economic and humanistic impact of NUCALA as compared to omalizumab (e.g., Page 34, Last Paragraph). Lacking is an appreciation of the differences between the models, including (Campbell model[17] vs. ICER model): treatment time horizon (5-year vs. lifetime); utility values (omalizumab trials vs. mepolizumab trials); mortality, responder analyses (all patients

and responders only vs. all patients). Additionally, GSK suggests revising the comparison of drug acquisition costs on Page 34; specifically providing the annual cost of omalizumab using 2015 WAC price[18] ($908.99/vial), which translates to an annual cost of $32,669.10 ($908.99/vials * 35.94 vials/year – Campbell estimated annual utilization rate[17]) which is significantly greater than the currently stated drug acquisition cost of ~$20,000 on Page 34.

Clarity of Approach: Clarity with respect to appropriate cost-effectiveness thresholds.

GSK believes that the thresholds employed by ICER (i.e., $50K/$100K/$150K) may be too low based on the economic literature.[19] The treatment population for NUCALA includes patients in their productive years or patients about to enter their productive years. The CEA literature on QALYs for the employed tends to find threshold values closer to $300,000/QALY and the willingness-to-pay literature includes estimates ranging from $160,000–260,000.[20,21,22]

GSK acknowledges the role of perspective on interpretation of model results. While the payer perspective is the stated objective from ICER, the societal perspective (e.g., inclusion of indirect costs associated with lost productivity [work and non-work]) may be equally important for health care decision makers. This is especially true for asthma, where published literature suggests that the indirect costs of asthma are nearly equivalent to the direct costs of treating the condition.[23,24] Exclusion of the indirect benefits of treating severe asthma may result in an understatement of the benefits of NUCALA.

Additional Points of Consideration:

- Definition of the appropriate patient population and administration of NUCALA should be consistent with FDA prescribing information. [25]
    - All Voting Questions: Revise phrase *"for patients with severe eosinophilic asthma"* to *"for patients with severe asthma and with an eosinophilic phenotype (as per prescribing information)."*
    - Page ES2, 1st Para, Last Sentence: Revise *"Office administration is required in order to monitor patients for hypersensitivity reactions, a common practice following administration of biologic agents."* to *"NUCALA should be reconstituted and administered by a healthcare professional. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended."*

Thank you for the opportunity to provide comments. We appreciate the difficulty of the work undertaken by the ICER team to synthesize over 12 years of research into a digestible summary. As is the nature of drug development, GSK has provided requested data as transparently and freely as allowed. We look forward to sharing even more data related to NUCALA as it becomes available.

Regards,

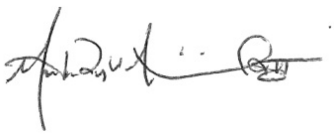

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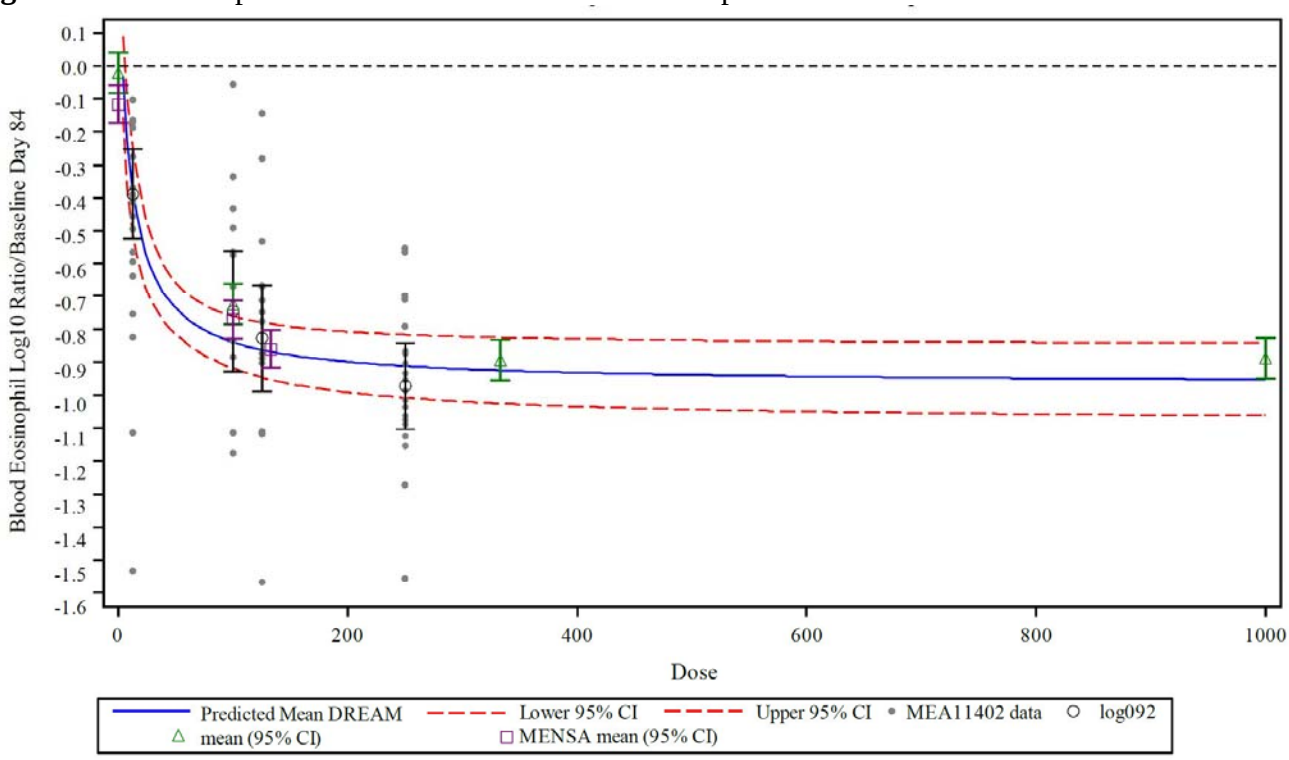
Figure 1: Dose Response Ratio to Baseline Blood Eosinophils[6]



DREAM = Dose Ranging Efficacy And safety with *Mepolizumab*; MENSA = *MEpolizumab* as adjunctive therapy iN patients with Severe Asthma; SE = standard error

Note: IV dose displayed=SC dose equivalent (i.e. IV dose/0.75 based on assumed bioavailability (estimate from study 018)) Note: 'log092'=Baseline-adjusted least square mean estimate (95% CI) from 092 study.

FINAL: January 12, 2016

PREPARED FOR: California Technology Assessment Forum (CTAF)
BY: Institute for Clinical & Economic Research (ICER**)**
REPORT TITLE: Mepolizumab (Nucala ®, GlaxoSmithKline plc.) for the Treatment of Severe Asthma with Eosinophilia: Effectiveness, Value and Value-Based Price Benchmarks
DATE OF DRAFT REPORT: December 21, 2015
COMMENT DEADLINE: January 12, 2015, 8 PM EST
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Section	Page and/or Line Number	Comment and/or revised language
General		The attached information is supplied in response to an open public comment period.
2. The Topic in Context/ Mepolizumab	Page 5/ Paragraph 4	Recommend changing "The Food and Drug Administration (FDA) approved mepolizumab for the treatment of severe eosinophilic asthma in November 2015" to "In November 2015, The Food and Drug Administration (FDA) approved mepolizumab for the treatment of severe eosinophilic asthma in patients aged 12 years and older"
6. Comparative Value/ Model Parameters	Page 20	Suggest providing additional details on how clinical trial data was extrapolated beyond the length of the randomized clinical trials timeframe in the model • Randomized clinical trial data was collected for 20-32 weeks. The report does not contain a description on disease progression function, and how data was extrapolated to a lifetime horizon
6. Comparative Value/Cost	Page 24/ Paragraph 2	Recommend including data/references to describe the cost implications for asthma patients with chronic oral corticosteroid (OCS) use • The annual OCS cost reference is from systematic lupus erythematosus
6. Comparative Value/ Utilities	Page 25/ Paragraph 2	There is a potential for lack of comparability with other competitor products due to mapping between mean total St George's Respiratory Questionnaire (SGRQ) scores and the European Quality of Life-5 Dimensions, as most of the other biologics (e.g. omalizumab, benralizumab, etc.) do not include SGRQ in their

		severe asthma pivotal trials
6. Comparative Value/ Utility	Page 25/ Paragraph 4	Recommend including a reference for the disutility of chronic OCS to provide clarity on how this number was calculated

Asthma and Allergy Foundation of America (AAFA)
Comments Regarding the Institute for Clinical and Economic Review (ICER) Draft Report on Nucala® (Mepolizumab) for Asthma

Key Issues and AAFA's Recommendations

We offer comments that address specific issues in the ICER report as well as comments that we believe may improve future analyses. As an organization that represents the voice of patients with asthma and allergic disease, our comments reflect our underlying belief that patients, and the patient perspective on matters of value, are recognized as important inputs to research and analysis relevant to asthma, and given appropriate weight in (for example) analyses that speak to the value of alternative approaches to care. As a result, our comments focus on:

- Assuring that the patients' voice is adequately captured and appropriately weighted in analyses of value;
- Assuring that analysis of the cost part of the value equation reflects costs as patients perceive them;
- Recognizing that we do not lose sight of the opportunities that exist to improve outcomes for patients with asthma, through improvements in "Standard of Care."

Capturing the patients' voice in analyses of value

AAFA believes that analyses of value must begin with an understanding of the outcomes that matter most to patients, and that that, in turn, implies the need to capture and weight patient-sourced data that describe outcomes that patients agree are relevant to them.

Given that, we want first to communicate our concern that the framework that we assume guided this work (and will guide ICER's work in the future) appears to have been constituted with little input from patients. We note that the group that provided input to the development of the ICER value assessment framework[1] included six payers and eight organizations representing manufacturers—but only one organization representing patients. And we believe, additionally, that that organization—Families USA, one that we respect greatly—would agree that it does not have the deep understanding of the needs and values of people with asthma, to be able to inform an assessment of value that adequately reflects patient needs.

We acknowledge that patient outcomes data were included in the ICER analysis—as these data were collected in the clinical trials upon which the work draws. That said, we are concerned that the impact of these inputs to the analysis may have been limited, given that that analysis appears primarily to have been configured to assess outcomes as payers see and value them.

Given these considerations, we recommend that:

- In revisions to this report and in analyses that ICER and others undertake in the future, efforts are made to bring the voice of patients more directly to the design of the methodology. AAFA is fully prepared to assist in those efforts.
- An effort is made to further evaluate the set of instruments available to capture patients' perspectives on Quality of Life—or the more general set of outcomes that are relevant to how patients with asthma perceive the value of care—and that the output of that evaluation guides the use of instrumentation for future analyses. Clearly, as ICER's (secondary) analyses often depend upon data collected by others for other (primary) analyses, it will be important to drive the use of preferred instruments into those primary analyses

(e.g., industry-sponsored clinical trials). We believe this is consistent with the intent of the FDA's Patient-Focused Drug Development initiative, and will serve to accelerate efforts to realize the intent of that initiative. We note, finally, that our recommendation seems to be well aligned with a group of experts called together to evaluate asthma Quality of Life instruments, whose summary in 2012 included "(r)esearch is strongly recommended to develop and evaluate instruments that provide a distinct, reliable, measure of the patient's perception of QOL, and important outcome that is not captured in other outcome measures."[2] Perhaps there is an opportunity to leverage the progress this group made to move this important work forward.

To the extent that that evaluation of current instrumentation reveals gaps—issues of great importance to people with asthma that are not adequately assessed by any instrument currently extant—we recommend investment in the development of measures and instruments that accomplish that assessment; and the expedited use of them in analyses that attempt to assess "value."

AAFA is fully prepared to participate in national efforts to assure that there are valid and reliable methods to assess the outcomes that matter to patients with asthma, and in fact eager to bring its registry development efforts to support the capture of data that a broad group of stakeholders (including patient organizations like AAFA, but also methodologists, researchers, providers, payers and manufacturers) suggest may be required to bring the patient voice reliably and cost-effectively to this work.

Analyzing costs as patients experience them

The ICER report evaluates cost from the perspective of the health care payer, including the perspective of society that ultimately must make decisions not only about investments in health care, but investments in other goods and services that matter to Americans. Without disputing the importance of these perspectives, we want to make clear that the costs that patients with asthma face—and therefore the "value" that mepolizumab may or may not represent to them—are quite distinct from the costs that payers and society as a whole face.

It is important both that the report (and future reports like it) make that clear, and make some effort to consider the out-of-pocket costs that patients with asthma face. We recommend that:

- The report specifically calls out the issue of cost from the patient perspective and, as possible, includes data that speak to the costs that patients face. ICER is to be commended for including Appendix C that provides data about payer coverage policies. To the extent that it were possible to translate those policies into "expected" (or "typical") costs for patients with eosinophilic asthma, readers of the report may have a much better sense of the challenges that those who are expected to benefit from mepolizumab are likely to face, realizing that benefit.
- ICER consider supplementing its outputs, to include models where the cost inputs are the costs patients face (rather than the costs payers face). Acknowledging that the level of effort here may be non-trivial, we believe that it would provide important information—and send an important signal—about value as patients who are expected to benefit from mepolizumab see it.
- There be additional exploration of issues related to the total economic burden of asthma, and on options to address that;
- There be additional public policy research, to explore options regarding prescription drug pricing that will promote affordability while continuing to provide the incentives to manufacturers that are needed to stimulate further innovation;
- There be investment in efforts to develop tools to help patients understand the cost and value of different therapeutic options available to them;
- That there be continued investment in efforts to assure coverage and reimbursement for evidence-based treatments beyond pharmaceuticals:

- Treatment options in accordance with the Guidelines for the Diagnosis and Management of Asthma (Expert Panel Report 3, EPR-3);
- Educational and preventive services conducted by clinicians, health educators, and other health and allied professionals both within and outside of the clinical setting;
- Home-based multi-trigger, multicomponent intervention and prevention services to help reduce and/or remediate asthma triggers in homes and schools.

Improving the "Standard of Care" (SoC)

We are struck by a finding in the report (that we acknowledge is not central to it), and by a significant literature that establishes that—for patients with asthma as with so many other chronic conditions—there is a gap (or a chasm) between what we **know** and what we **do**: between the outcomes that could be achieved if the science that we have were consistently and reliably implemented, and the outcomes we observe in the real world.

The finding in the report that we would like to highlight (on page 16 of the Executive Summary) relates to the observation that "there was a marked decrease in the annual rate of asthma exacerbations in the placebo group of the MENSA trial;" in fact, that "marked reduction (was) greater than the difference…between the mepolizumab and placebo groups." While the authors note—and we agree—that we may be seeing some regression to the mean here, they also suggest the possibility that this improvement may reflect "optimization of the standard of care, highlighting the potential benefits of greater attention to maximizing adherence to standard therapy in patients with severe asthma."

We believe that point needs to be called out and further discussed, and would recommend that it receive further attention in the final report. In the national conversation about new and high cost drugs, we are concerned that others may lose sight of the fact that there is the opportunity to make investments in what may be very cost-effective policies, strategies and tactics that do "no more than" improve "Standard of Care" for patients with chronic conditions—and that these represent an important alternative track to creating value. For asthma, that may mean:

- Investing in patient education and tools and strategies that promote more effective patient self-management;
- Investing in—and reimbursing for—strategies and tactics that reduce exposure to triggers (for example, home assessment and remediation);
- Revising payment policies, to maximize access to lower cost treatments which would lead to improve outcomes—if patients could afford them;
- Developing a deeper understanding, and solutions based on that deeper understanding, about what barriers to care patients with severe asthma face.

While recognizing the strength of the work summarized in the report, AAFA believes that there are opportunities to increase its relevance and value. In particular, we have highlighted in our comments ways that we believe the report can help to capture—or at least to signal the importance of capturing in future reports—the patients' perspective on both the cost and the quality/outcome elements of the value equation. And we have highlighted the opportunity for the report to consider the potential value of an obvious (but often unconsidered) use of funds; namely to improve "Standard of Care" through a set of interventions that are likely to prove to be quite cost effective.

[1] http://www.icer-review.org/wp-content/uploads/2014/01/Slides-on-value-framework-for-national-webinar1.pdf; slide 4.
[2] Wilson SR, Rand CS et al. Asthma Outcomes: Quality of Life. J Allergy Clin Immunol 2012; 129: S88-S123.

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January 14, 2016

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RE: Draft Report on Nucala (Mepolizumab) for Asthma

Dear ICER Colleagues:

On behalf of the 15,000 members of the American Thoracic Society, I appreciate the opportunity to comment on ICER's draft report on Nucala (Mepolizumab) for Asthma. The ATS is a medical professional society of clinicians, scientists and allied health professionals dedicated to the prevention, detection, treatment and cure of pulmonary disease, critical care illness and sleep disordered breathing. Our members have unique experts in the diagnosis and management of asthma. As such, the ATS has a keen interest in ICER's report.

The ATS offers the following comments:

ATS members have conducted pioneering fundamental research and clinical studies into the mechanisms and consequences of eosinophilic airway inflammation, and have been at the forefront of clinical research of interleukin 5 (IL-5) targeted therapies. In addition, several ATS members served on the FDA Pulmonary and Allergy Drug Advisory Committee that voted unanimously in favor of approving mepolizumab (anti-IL-5) for adults with severe asthma. Therefore, the ATS is very familiar with the totality of data supporting the safety and efficacy of mepolizumab in severe asthma. This includes not only the two pivotal efficacy studies referred to in the ICER report, but also dose finding studies and other pre-clinical research. This drug will be an important part of our armamentarium, and I urge CTAF panel members to strongly endorse its approval.

My physician colleagues and I are in urgent need of new therapies for our patients with severe eosinophilic asthma, especially those who experience frequent exacerbations and suffer from the disabling side effects of chronic corticosteroid use.

There are millions of patients with these features of asthma, who remain severely symptomatic despite the use of other biologics (e.g. omalizumab), evidence-based treatment, and meticulous attention to avoiding asthma triggers and medication adherence and compliance. The approval of mepolizumab marks the beginning of a new era of targeted therapeutics for exactly this subset of severe asthmatics. The evidence supports the idea that mepolizumab reduces the frequency of disease exacerbations, reduces unwanted steroid side effects, and improves the quality of life for patients who have exhausted all other treatment options. ATS members and our patients are eagerly awaiting the arrival of mepolizumab in the clinic.

Specifically, the ATS believes that there is substantial evidence that the net health benefit of adding mepolizumab to standard of care is greater than that of standard of care alone. In addition, given the lack of other treatment options for this subset of severe asthmatics, the ATS feels that there is strong evidence supporting the care value and provisional health system value of adding mepolizumab to standard of care vs. relying on standard of care alone.

The ATS would like to address two additional points raised in the ICER report. First, the ICER report concluded that there was "moderate" efficacy supporting the use of mepolizumab, noting concerns about short study duration and sample size. The ATS disagrees with this conclusion and favors stronger wording in support of the drug. The ATS is reassured by the open label extension studies demonstrating a durable and sustained treatment effect for subjects receiving mepolizumab long-term. Taken together with recent studies demonstrating a very similar efficacy profile for other IL-5 antagonists (e.g. reslizumab, with ~50 percent reduction in exacerbation frequency), the ATS feels that the available evidence to-date suggests that mepolizumab will be extremely helpful for this targeted subgroup of eosinophilic asthmatics.

Second, the ICER report suggests there will be no long-term benefit of anti-IL-5 therapy, and that disease will return to baseline status after treatment is stopped. Although available evidence is currently lacking, the ATS thinks it is likely that by reducing airway eosinophilia, the regular use of mepolizumab will attenuate airway remodeling in at least some subjects with severe asthma. Airway remodeling refers to structural changes in the airway that occur in subjects with severe asthma over time, which results in loss of lung function and reduced responsiveness to commonly used asthma inhalers (e.g. beta agonists like albuterol). Extensive in vitro and animal model studies have implicated a key role for eosinophils in this process. No currently available therapies consistently prevent airway remodeling, and ATS members are pleased to have an entirely new class of agents that we think will have efficacy in this regard.

The pulmonary community has known for more than 100 years that airway eosinophilia is a hallmark of asthma, but until now we have had no way to specifically target this cell type. Reassuringly, the safety profile of mepolizumab appears excellent, and by precisely targeting the IL-5/eosinophil axis mepolizumab should have minimal effects on the adaptive immune system.

As president of the American Thoracic Society, I hope you will consider our comments as ICER finalizes its report.

Sincerely,

Atul Malhotra, M.D.
President
American Thoracic Society