NATIONAL FORUM
FOR HEART DISEASE & STROKE PREVENTION
1150 Connecticut Ave. NW, Ste. 300, Washington, DC 20036

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Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review
14 Beacon Street, Suite 800
Boston, MA 02108
Submitted Electronically: publiccomments@icer-review.org

Dear Dr. Pearson:

Thank you for the opportunity to comment on the draft review report, "Mavacamten for Hypertrophic Cardiomyopathy: Effectiveness and Value," dated August 18, 2021.

We appreciate ICER's willingness to review comments and recommendations from the National Forum's Value & Access Collaboration which works on these issues. The undersigned Value & Access Collaboration members, including patient, provider, payer, and public health organizations, jointly offer the following feedback for ICER's consideration in the development of the revised review report.

In conducting a cost-effectiveness analysis of mavacamten, ICER has taken on a large challenge given the lack of clinical, epidemiological, and cost data and uncertainty around it.

We were gratified that several of our recommendations for the scoping document were included in the draft report.

We respectfully offer the following recommendations:

Inputs

While we appreciate the inclusion in the narrative report of patient perspectives and results from the patient survey because patient experience bears on outcomes, we recommend that this information be included in the economic model dataset. Otherwise, patient perspectives may not be considered by payers that will use the economic model dataset when making coverage decisions.

ICER assumed static levels of four inputs which impact the model's utility:

1) Disease Progression
- ICER's model reflected the stoppage of disease progression after the initial few weeks of treatment.
    - This is inconsistent with Sarcomeric Human Cardiomyopathy Registry (SHaRe) data showing that the cumulative burden of HCM is substantial and dominated by

heart failure and atrial fibrillation occurring many years after diagnosis. Young age at diagnosis and the presence of a sarcomere mutation are powerful predictors of adverse outcomes. The findings highlight the need for close surveillance throughout life and to develop disease-modifying therapies.[1]

- According to the 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy (HCM), among referral-based cohorts of patients with HCM, 30% to 40% will experience adverse events, including: 1) sudden death events; 2) progressive limiting symptoms because of LVOTO (left ventricular outflow tract obstruction) or diastolic dysfunction; 3) HF (Heart Failure) symptoms associated with systolic dysfunction; and 4) AF (Atrial Fibrillation) with risk of thromboembolic stroke.[2]
- We suggest that this data be reflected in the model.

2) Mortality Rates

- ICER shows "mortality estimates were sourced from the CDC and reflect US average mortality rates adjusted for age and gender as reflected by the overall averages of baseline characteristics of patients seen in the clinical trial. Based on conversations with clinical experts and available evidence, mortality was assumed to be constant across NYHA class" (pg. 110). We would like to point out that:
  - SHaRe data shows the mortality of patients with HCM to be ≈3-fold higher than for the US general population at similar ages.[3]
  - Studies conducted at centers of excellence consistently demonstrate mortality negligibly different from that of the general population.[4]
  - Thus, we recommend that the quality of care provided and the level of clinical expertise available be given more consideration in ICER's analysis.

3) NYHA Class (pg. 22)

- The model held the proportion of alive patients in each NYHA class constant up to cycle 8. However, the disease course of HCM is not linear. Therefore, the model should reflect actual variance.
- There can be significant variability in a patient's NYHA class from one day to the next. This variability, together with the subjectivity of NYHA class determination, limits the validity of this metric to gauge therapeutic benefit.

4) Discontinuation of Therapy (pg. 22)

- Discontinuation was not included in the model. This is inconsistent with real-world experience. Data shows approximately one in five new prescriptions are never filled; of those filled, approximately 50% are taken incorrectly, particularly with regard to timing, dosage, frequency, and duration.[5] This should be accounted for in the model.

5.) Admission for Titration

- ICER refers to "other than an initial hospitalization associated with disopyramide" (see Table E10 – pg. 117). However, we do not see disopyramide listed in table E10.

Therefore, it is not clear whether the economic models assume hospitalization for titration of disopyramide or mavacamten. Studies have indicated that hospitalization for titration of disopyramide can be safely avoided.[6] This would have a major impact on cost-effectiveness results.

Comparators

Because the only mortality effect across treatments in the model was associated with perioperative mortality from myectomy and septal ablation and no other adverse effects, the benefit of these treatments compared to mavacamten is overestimated.

The draft evidence report ignores the fact that the 2020 ACC/AHA HCM Guidelines recommend that strong consideration be given to referral of patients with obstructive HCM, who are candidates for invasive SRTs, to established high-volume-primary or comprehensive HCM centers to perform procedures with optimal safety and benefits outcomes. This information should be reflected in the model.

Because the model was stopped at 32 weeks, the progression for longer term financial benefits could not be calculated. Thus, long term benefits are potentially underestimated as recent data shows results from treatment with mavacamten at 60 weeks are consistent with the parent study, EXPLORER-HCM.[7]

However, we note concern with serious event occurrences in the EXPLORER-HCM trial.[8] For example, the 6% of patients whose ejection fractions (LVEF) dropped below 50% would have to discontinue use of mavacamten, be followed more intensely, and require follow-up medical treatment. Thus, we recommend the model reflect harms which would impact both patient quality of life and cost.

Contextual Considerations and Potential Benefits

While ICER acknowledges lack of information from patients and caregivers of the potential benefits and limitations of the analyses in this report, these considerations are critical and impact patient care and decisions about treatment options and judgements of overall long-term value for money. The 2020 ACC/AHA Guidelines on HCM recommends (Class 1, Strong, B-NR) shared decision-making in developing a plan of care, including but not limited to decisions regarding genetic evaluation, activity, lifestyle, and therapy choices…" Accordingly, the Value & Access Collaboration recommends the contextual considerations that appear in voting questions 7-9 also appear in voting questions 1-4.

Cost-Effectiveness Analysis

We urge a degree of reconceptualization of the cost-effectiveness analysis. Given the variability of HCM and no specific scale for HCM patient assessment available, ICER needs to give more

attention to contextual data and patient perspective. In addition to NYHA class, we recommend ICER use the Kansas City Cardiomyopathy Questionnaire and research on patient perspectives in its analysis.

It is important to ask what society is "buying" with a new drug. Clinical indicators are, of course, critical, but from the patient perspective, what is being bought is at least twofold: symptom relief and worry relief. We note that in the draft report, per the online patient questionnaire, only 50.4% of patients felt that their treatment "worked well." The remainder found varying degrees of problems. Only 43% reported no side effects (pg. 46).

These figures indicate that there is an unmet need for improved therapies. In particular, the report notes that there is an unmet need for relief of exertional symptoms for patients who do not have access to specialized centers.

It would also be useful to distinguish the QALY impact of:
(1) clinical and symptom improvement;
(2) clinical improvements without apparent symptom improvement;
(3) symptom improvement without clinical improvement, and:
(4) clinical improvement without symptom improvement.

In the draft report, ICER states that it continues to work on obtaining data to allow for a modified societal perspective to be presented in the revised Evidence Report. We strongly encourage ICER to pursue its goal to perform the analysis from the societal perspective as this could capture and monetize significant contextual considerations.

Potential Budget Impact Analysis

- We recommend that the report include clinical effectiveness and cost effectiveness, and not budget impact. Some stakeholders have used budget impact analyses to justify access barriers for therapies whose cost is within ICER's recommended range. Payers can conduct their own budget analyses.
- The danger of projecting budgetary impact based on non-real world pricing assumptions and non-real world utilization rates is that it can trigger barriers to access to potentially cost-effective therapies. This has happened following release of other ICER reports.
- The risk of linking budget impact to recommended price ranges is that it could disincentivize innovation.

Access Considerations

As mentioned in ICER's report, access challenges remain for patients to obtain care at centers of excellence.

Study findings suggest inequities in clinical care provisions for HCM exist based on race and gender. Black patients with HCM experience inequities in care with lower use of invasive septal

reduction therapy and genetic testing compared with White patients. In addition, women with HCM are under-diagnosed and referred to centers later than men, often with more advanced heart failure.[9, 10]

ICER's analysis appears to assume that patients have access to the full range of treatment options and high-quality care. A considerable portion of the population does not have access to centers of excellence. This limits both options and quality of care. We believe that geographic availability of therapies and care should be factored into the model as well.

Determination of appropriate intervention for individual patients should be made by the patient and their physician. Mavacamten could offer an alternative for patients who do not respond to first-line therapy, or who are ineligible or high-risk for invasive therapy, or who do not have access to centers of excellence.

Again, thank you for your consideration. We look forward to reviewing and providing additional comments throughout the review process.

Sincerely,

Members of the Value & Access Collaboration representing the following organizations:

National Forum for Heart Disease & Stroke Prevention (convener)
American Association of Heart Failure Nurses
American College of Cardiology
American Heart Association
American Pharmacists Association Foundation
American Society for Preventive Cardiology
Association of Black Cardiologists
Association of State and Territorial Health Officials
BallengeRx Consulting
Global Healthy Living Foundation
Hypertrophic Cardiomyopathy Association
Independent Health
Institute for Patient Access
Mended Hearts
National Alliance of Healthcare Purchaser Coalitions
Partnership to Advance Cardiovascular Health
Partnership to Improve Patient Care
Preventive Cardiovascular Nurses Association
University of Michigan Center for Value-Based Insurance Design
WomenHeart

[1] Genotype and Lifetime Burden of Disease in Hypertrophic Cardiomyopathy Insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe). Ho CY, Day SM, Ashley A, Circulation 2018 Oct 138;14. https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.117.033200

[2] 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Ommen SR, Mital S, Burke MA Circulation. 2020;142:e558–e631 https://doi.org/10.1161/CIR.0000000000000937

[3] Genotype and Lifetime Burden of Disease in Hypertrophic Cardiomyopathy Insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe). Ho CY, Day SM, Ashley A, Circulation 2018 Oct 138;14. https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.117.033200

[4] Hypertrophic Cardiomyopathy in Adulthood Associated with Low Cardiovascular Mortality with Contemporary Management Strategies. Jrnl Am Coll Cardiology 2015: 18. DOI: https://doi.org/10.1016/j.jacc.2015.02.061

[5] Grand Rounds: Improving Medication Adherence for Chronic Disease Management — Innovations and Opportunities. MMWR Morb Mortal Wkly Rep 2017:66. DOI: http://dx.doi.org/10.15585/mmwr.mm6645a2

[6] Safety of Outpatient Initiation of Disopyramide for Obstructive Hypertrophic Cardiomyopathy Patients. Jrnl Am Heart Assoc. 2017:6, DOI: 10.1161/JAHA.116.00515220

[7] Long-term Safety of Mavacamten in Patients with Obstructive Hypertrophic Cardiomyopathy: Interim Results of the MAVA–Long-term Extension (LTE) Study Rader, F, Choudhur L, Saberi S. et al Poster presented at the American College of Cardiology (ACC) Virtual 70th Annual Scientific Session & Expo; May 15-17, 2021.

[8] Mavacamten for Treatment of Symptomatic Obstructive Hypertrophic Cardiomyopathy (EXPLORER-HCM): a Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial. Olivotto I, Oreziak A. Barriales-Villa R et al. Lancet. Lancet 2020; 396: 759–69. https://doi.org/10.1016/S0140-6736(20)31792-X

[9] Association of Race With Disease Expression and Clinical Outcomes Among Patients with Hypertrophic Cardiomyopathy. Eberly LA, Day SM, Ashley EA, et al. JAMA Cardiol. 2020;5(1):83–91. doi:10.1001/jamacardio.2019.4638

[10] Impact of Sex on Clinical Course and Survival in the Contemporary Treatment Era for Hypertrophic Cardiomyopathy. Rowin EJ, Maron MS, Wells S et. al Journal of the American Heart Association. 2019;8:e012041 https://doi.org/10.1161/JAHA.119.012041