Bristol Myers Squibb™

June 10, 2024

Re: Draft Evidence Report "Imetelstat for Anemia in Myelodysplastic Syndrome: Effectiveness and Value"

Submitted electronically via: publiccomments@icer.org

Dear ICER Review Team,

Bristol Myers Squibb (BMS) acknowledges the importance of fully and accurately understanding the value that innovative therapies provide to patients, and we appreciate the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) draft evidence report titled "Imetelstat for Anemia in Myelodysplastic Syndrome: Effectiveness and Value." At BMS, we are inspired by a single vision—transforming patients' lives through science. Our mission is aimed towards discovery, development and delivery of innovative medicines that help patients prevail over serious diseases.

In response to ICER's summary of luspatercept stating that "Luspatercept was recently approved as a first-line treatment for lower-risk MDS patients with anemia, and is particularly effective in patients with ring sideroblasts (RS+, approximately 35% of the MDS population)" BMS would like to clarify that Reblozyl is FDA-approved for first line low-risk MDS treatment regardless of RS status based on the ITT population analysis of the COMMANDS trial.[1,2] The COMMANDS trial was not powered to detect a difference between RS subgroups and caution should be used when comparing unpowered subgroups.

Below are further comments in response to specific ICER statements within the draft evidence report of this ICER assessment.

1. **BMS recommends a re-examination of clinical data inputs.**

    - Regarding "Comparative Clinical Effectiveness," BMS acknowledges the challenges in performing comparisons based on available published data by RS status. Specifically, stratified analyses on safety and modified hematologic response-erythroid (mHI-E) were not conducted, and this brings substantial limitations to the analysis and conclusions.

2. **BMS suggests modifications are needed regarding the referenced economic data.**

    - Regarding "Patient and Caregiver Perspectives," BMS acknowledges the individual patient experience on luspatercept but recommends further contextualizing the patient quote by including information on out-of-pocket (OOP) costs for the majority of patients and the availability of copay assistance programs. This singular patient quote is not reflective of the overall patient experience in the United States. Currently,

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93%* of commercially insured and 90%† of Medicare patients are paying $0 for their luspatercept prescription ($0 copay). BMS is committed to ensuring the diverse patient voice and perspective is appropriately and meaningfully represented; it is of utmost importance that all eligible patients have access to our medicine. We encourage patients to leverage applicable BMS or third-party copay assistance programs. Through BMS Access Support®, patients can receive information on financial assistance programs that may be available to them.

- Regarding "Long-Term Cost Effectiveness," BMS recommends:
  - Conducting a probabilistic sensitivity analysis. The <0.5% difference in total costs between luspatercept and imetelstat in ICER's cost-effectiveness model is within the uncertainty range that we would typically observe within health economic assessments and warrants further exploration.
  - Including myeloid growth factors as a component of the cost effectiveness model. Myeloid growth factors were used in a substantial proportion of patients in the imetelstat arm of the IMerge trial (35% vs 3% in placebo arm)[3] and were omitted from supportive care costs in the cost-effectiveness model. Due to the important safety concerns and associated costs, BMS feels strongly that this should be included.
  - Conducting the analysis to include the predicted $25,000/month[4], or $300,000/year. Given recently released imetelstat pricing information, a scenario analysis would negate the negligible total cost savings of imetelstat as reported in ICERs budget impact and cost-effectiveness models.
    - We also encourage ICER to consider the increased final price of imetelstat which was communicated verbally during Geron's Conference Call following the FDA-approval of imetelstat.[5]

*OOP distribution data cost average includes prescriptions filled from January 2023 to December 2023 from Symphony Health Solutions (SHS) Remittance Claims Data and reflects any financial assistance that was used. "Commercially Insured Patients" is inclusive of commercially insured patients eligible and receiving assistance through the BMS Access Support Co-Pay Assistance Program. Some patients may pay more than the cost listed above.

†OOP distribution data cost average includes prescriptions filled among Medicare Part B and Medicare MA/PD patients, January 2023 to December 2023 from SHS Remittance Claims Data and reflects any financial assistance that was used. "Medicare Patients" are not eligible for the BMS Access Support Co-Pay Assistance Program but may be eligible for other forms of third party co-pay assistance. Some patients may pay more than the cost listed above.

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Thank you for the opportunity to review and comment on this draft evidence report.

Sincerely,

Anthony Barisano, PharmD
Vice President | WW Health Economics & Outcomes Research – Hematology & Oncology

References:

1. Bristol Myers Squibb. Press Release: U.S. FDA Approves Bristol Myers Squibb's Reblozyl® (luspatercept-aamt) as First-Line Treatment of Anemia in Adults with Lower-Risk Myelodysplastic Syndromes (MDS) Who May Require Transfusions. Available at: https://news.bms.com/news/details/2023/U.S.-FDA-Approves-Bristol-Myers-Squibbs-Reblozyl-luspatercept-aamt-as-First-Line-Treatment-of-Anemia-in-Adults-with-Lower-Risk-Myelodysplastic-Syndromes-MDS-Who-May-Require-Transfusions/default.aspx
2. Reblozyl® (luspatercept-aamt) [prescribing information]. Celgene Corporation, a Bristol Myers Squibb Company; August 2023.
3. Zeidan AM, Santini V, Platzbecker U, et al. Efficacy of imetelstat on red blood cell (RBC)-transfusion independence (TI) in the absence of platelet transfusions or myeloid growth factors in IMerge. Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting, May 31–June 4, 2024, Chicago, IL. Presentation 6566.
4. Geron. May 2024 Corporate Presentation. Accessed May 28, 2024. https://s201.q4cdn.com/710325604/files/doc_presentations/2024/May/01/geron-corporate-deck-may-2024-final-v2.pdf
5. Geron. RYTELO™ (imetelstat) FDA Approval Conference Call. Accessed June 7, 2024. https://s201.q4cdn.com/710325604/files/doc_presentations/2024/06/RYTELO-FDA-Approval-IR-Slides-FINAL.pdf

PIPC Partnership to Improve Patient Care

June 10, 2024

Sarah K. Emond, MPP
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Dear Ms. Emond,

The Partnership to Improve Patient Care (PIPC) appreciates the opportunity to comment on the Institute for Clinical and Economic Review (ICER) assessment on anemia in myelodysplastic syndrome.

Myelodysplastic syndromes are a group of rare, underrecognized, and under diagnosed bone marrow failure disorders. Most patients have anemia when they are diagnosed. This leads to extreme fatigue that can have a meaningful impact on patient quality of life.[1]

PIPC encourages ICER to consider the following comments as it revises its model.

ICER oversimplifies health states, including undervaluing the effect of treatment.

The model assumes that if a patient stops responding to treatment during any cycle in the model, then that patient returns to the transfusion dependance state in which they began - either low or high burden transfusion dependence states, versus contemplating that the patient could have moved from high dependence to low dependence. The model similarly assumes that those who do not respond to treatment in the high transfusion dependance state cannot move to the low transfusion dependance state. This simplification likely underestimates the value of the interventions being evaluated, as it is possible that patients could move and stay in a low dependence state, which would be valuable to the patient. ICER should take a more nuanced view on this topic and capture movement from high to low dependence states.

ICER's model should include non-drug costs for ongoing treatment of MDS.

As portrayed, the ICER model does not seem to include non-drug costs for ongoing treatment of MDS in either transfusion independent or transfusion dependent health states other than the cost of adverse events. The methods section for the cost-effectiveness model doesn't refer to any costs being applied to time spent in the first three states of the model. It details the estimated cost of each drug being evaluated, drug utilization, best supportive care costs, and health state costs for high risk MDS and acute myelogenous lymphoma. It does not however describe how health state costs for the states of high burden and low burden transfusion independence and transfusion dependence are calculated.

[1] https://www.mds-foundation.org/what-is-mds/

Even if we assume that best supportive care costs would be applied to all patients in these three states equally, this does not accurately represent benefit of treatment. The goal of the drugs under evaluation is to keep patients in transfusion independent states instead of transfusion dependent states. Transfusion independent states are not only better for patients, but they are significantly less costly, which should be captured in the model.

Estimates from the literature suggest that marginal differences in overall direct healthcare costs differ between transfusion dependent and transfusion independent lower-risk MDS patients by between $54,264 per year[2] and $157,198 per year.[3]

ICER uses a health care perspective for its base case when it should be using the societal perspective.

MDS is a disease that creates significant caregiver burden. The value of a treatment that could reduce this burden should be reflected in any value assessment for these treatments. When the impact on caregivers and social care costs is high, as in MDS, the societal perspective is always the most appropriate base care. Many leaders in HTA, like the National Institute for Health and Care Excellence (NICE) have already taken the step of caregiver utility in its cost-effectiveness models for diseases such as Alzheimer's, MS and Parkinson's disease.[4] It is also the recommended perspective for cost-effectiveness models of the second panel on cost-effectiveness[5], and ISPOR.[6] PIPC encourages ICER to replace a purely health care perspective with a broader societal perspective for its base case analysis.

ICER Continues to Use the Discriminatory QALY and the Similar Measure evLYG.

Multiple studies have shown that cost-effectiveness models using the quality-adjusted life year (QALY) discriminate against patients with chronic conditions,[7] and people with disabilities.[8] There is widespread recognition that the use of the QALY is discriminatory, reflected in laws that bar its use in government decision-making. The National Council on Disability (NCD), an independent federal agency advising Congress and the administration on disability policy, concluded in a 2019 report that QALYs discriminate by placing a lower value on treatments which extend the lives of people with chronic illnesses and disabilities. NCD recommended that policymakers and insurers reject QALYs as a method

[2] Frytak JR, Henk HJ, De Castro CM, Halpern R, Nelson M. Estimation of economic costs associated with transfusion dependence in adults with MDS. Current medical research and opinion. 2009 Aug 1;25(8):1941-51.
[3] DeZern AE, Binder G, Rizvi S, Corvino FA, Arikian SR, Surinach A, Lee J, Smith BD. Patterns of treatment and costs associated with transfusion burden in patients with myelodysplastic syndromes. Leukemia & Lymphoma. 2017 Nov 2;58(11):2649-56.
[4] Afentou N, Jarl J, Gerdtham UG, Saha S. Economic evaluation of interventions in Parkinson's disease: a systematic literature review. Movement disorders clinical practice. 2019 Apr;6(4):282-90.
[5] Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, Kuntz KM, Meltzer DO, Owens DK, Prosser LA, Salomon JA. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. Jama. 2016 Sep 13;316(10):1093-103.
[6] Garrison Jr LP, Mansley EC, Abbott III TA, Bresnahan BW, Hay JW, Smeeding J. Good research practices for measuring drug costs in cost-effectiveness analyses: a societal perspective: the ispor drug cost task force report—Part II. Value in Health. 2010 Jan;13(1):8-13.
[7] Paulden M. Recent amendments to NICE's value-based assessment of health technologies: implicitly inequitable?. Expert review of pharmacoeconomics & outcomes research. 2017 May 4;17(3):239-42.
[8] Nord E, Pinto JL, Richardson J, Menzel P, Ubel P. Incorporating societal concerns for fairness in numerical valuations of health programmes. Health economics. 1999 Feb;8(1):25-39.

of measuring value for medical treatments.[9] The recent nondiscrimination regulations governing Section 504 of the Rehabilitation Act also bar the use of discriminatory measures such as QALYs in decisions impacting access to care among entities receiving federal financial assistance.

We share the concerns of NCD about the equal value of life year gained (evLYG), a similar measure created by ICER to supplement the QALY. The evLYG is a simplistic fix attempting to address criticism that the QALY devalues life years lived with a disability, yet it fails to account for oversimplified measures of quality-of-life gains in expected life years and it does not account for any health improvements in extended life years. Like the QALY, the evLYG relies on average estimates based on generic survey data and obscures important differences in patients' clinical needs and preferences, particularly those with complex diseases and from underrepresented communities.[10] It assumes that people value life year gains more than quality of life improvements, giving a lower value to health interventions for patient populations that have a lower life expectancy or fewer life years gained from treatment, which may include people with disabilities, underlying chronic conditions, older adults, and certain communities of color.[11] With the evLYG and the QALY, ICER promotes two compromised and flawed measures of health gain. Deciding which to choose is confusing and inconsistent.

Conclusion

ICER continues to fail to capture actual value of treatment to patients by oversimplifying health states, utilizing a health care perspective as its base case, and relying on the discriminatory QALY. PIPC urges ICER to revisit some of its dated modeling constructs and work to more accurately capture value to the patient population in question.

Sincerely,

Tony Coelho
Chairman
Partnership to Improve Patient Care

[9] https://www.ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf
[10] DiStefano MJ, Zemplenyi A, Anderson KE, Mendola ND, Nair KV, McQueen RB. Alternative approaches to measuring value: an update on innovative methods in the context of the United States Medicare drug price negotiation program. Expert Rev Pharmacoecon Outcomes Res. 2024 Feb;24(2):171-180. doi: 10.1080/14737167.2023.2283584. Epub 2024 Jan 25. PMID: 37961908.
[11] Mike Paulden, Chris Sampson, James F. O'Mahony, Eldon Spackman, Christopher McCabe, Jeff Round, Tristan Snowsill, Logical Inconsistencies in the Health Years in Total and Equal Value of Life-Years Gained,
Value in Health, Volume 27, Issue 3, 2024, Pages 356-366.