Iptacopan and Danicopan for Paroxysmal Nocturnal Hemoglobinuria:

Final Policy Recommendations

March 13, 2024

Prepared for

Policy Recommendations

Introduction

The following policy recommendations reflect the main themes and points made during the Policy Roundtable discussion at the February 16, 2024 CTAF public meeting on the use of iptacopan and danicopan for the treatment of Paroxysmal Nocturnal Hemoglobinuria. At the meeting, ICER presented the findings of its revised report on these treatments and the CTAF voting council deliberated on key questions related to their comparative clinical effectiveness, potential other benefits and contextual considerations, and long-term value for money at current prices. Following the votes, ICER convened a Policy Roundtable of two patients, two clinical experts, two payers, and zero representatives from a pharmaceutical manufacturer to discuss how best to apply the evidence and votes to real-world practice and policy. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants.

A recording of the conversation can be accessed here (part one) and here (part two), and a recording of the voting portion of the meeting can be accessed here. More information on Policy Roundtable participants, including conflict of interest disclosures, can be found in the appendix of this document. ICER's report on these treatments, which includes the same policy recommendations, can be found here.

The roundtable discussion was facilitated by Dr. Steven Pearson. The main themes and recommendations from the discussion are organized by audience and summarized below.

All Stakeholders

Recommendation 1

All stakeholders have a responsibility and an important role to play in ensuring that effective treatment options for patients with PNH are introduced in a way that will help reduce health inequities.

Safe and effective treatment for PNH should not be limited by excessive cost or other barriers to appropriate access to care. Efforts are needed to ensure that existing and new therapies for PNH, including C5 inhibitors, pegcetacoplan, iptacopan, and add-on danicopan (if approved), improve the health of patients without aggravating existing health inequities. Clinical experts and patients highlighted that the high cost of therapies may worsen disparities in accessing care. This may be due to lack of health insurance that limits access to new therapies prescribed, or steep out-of-pocket costs, which may be exacerbated when oral treatments are covered under the

pharmaceutical benefit within an insurance plan as opposed to intravenous medications covered under the medical benefit. The cost of care is not the only factor that may contribute to health inequities. Patients and clinical experts noted that because PNH is a rare disease, hematologists with clinical expertise in the condition are often clustered in academic settings, leaving patients in underserved rural and urban areas without adequate access. Structures and policies to foster home infusion of IV therapies, travel for patients when needed, and remote collaboration between clinicians, are needed to address these barriers to appropriate care and to maximize the potential of new oral agents to reduce health inequities.

To address these concerns:

State and federal policy makers should take the following actions:

- Issue legislation to promote telehealth, such as the Creating Opportunities Now for Necessary and Effective Care Technologies (CONNECT) for Health Act of 2023 (H.R. 4189) that is being considered for Medicare beneficiaries which proposes to permanently remove all geographic restrictions that would enable the limited number of PNH specialists to advise local hematologists in regions of the country lacking this highly specialized expertise.

- Promote digital health equity through legislation, such as the Lifeline Program or the Emergency Broadband Benefit, that supports smartphone ownership and reduce broadband costs for low-income individuals.

Manufacturers should take the following actions:

- Set the price for new treatments in fair alignment with added benefits for patients.

- Provide advice and support for patients with PNH, such as assigning a case manager to help patients and families access therapies and to assist with insurance benefits navigation.

Payers should take the following actions:

- Reduce administrative burden and streamline the process to arrange for home infusion therapy for C5 inhibitors for patients who prefer this option and/or do not have easy access to an infusion center.

- When administering site of service (SOS) policies to ensure C5 inhibitors are infused in low-cost settings, patients should not be held liable for any added out-of-pocket costs and should be eligible to share in the savings realized by health plans.

- In developing coverage policies, ensure newer oral therapies have an equitable out-of-pocket cost burden under the pharmaceutical benefit compared to existing C5 inhibitors covered under the medical benefit. This is critical to make sure that the financial burden is

not driving treatment choices, particularly for patients who do not live near an infusion center or cannot arrange home infusions.

Payers

Recommendation 1

Payers should be aware of several key issues regarding the treatment landscape for PNH: 1) patients and clinicians have become accustomed to and are satisfied with an intravenously administered C5 inhibitor as frontline therapy in treatment-naïve patients; 2) clinicians do not have prediction models or biomarkers to identify which patients treated with a C5 inhibitor will develop clinically significant extravascular hemolysis (cs-EVH) nor distinguish which switch or add-on proximal complement inhibitor for this population is best; and 3) there is a high value placed on individual shared decision making for patients choosing between a C5 inhibitor and non-intravenous treatment options.

Historically, payers have not employed active utilization management policies for PNH, an approach which likely reflects the limited treatment options before the availability of newer proximal complement inhibitors. Clinical experts suggested that clinicians and patients have generally expressed a 'wait-and-see' approach until longer-term evidence on the safety and effectiveness is accrued as to whether the newer monotherapy proximal complement inhibitors, including pegcetacoplan and iptacopan, will have the same durable protection against breakthrough hemolysis and thrombosis as C5 inhibitors. Given the inability to predict which patients will develop cs-EVH when treated with a a C5 inihibitor or to identify which switch or add-on proximal complement inhibitor will work best for this subpopulation, both clinical experts and patient experts emphasized that patients and clinicians place a high value on shared decision-making given the important trade-offs in potential harms and benefits of the different options.

Recommendation 2

Annual coverage renewal requirements for PNH therapies should either be eliminated or implemented using a separate time-sensitive pathway to avoid missing doses, and should not penalize improvement on therapy as a reason for denial of continued coverage.

Since symptomatic and high-risk patients with PNH require indefinite therapy to prevent the untoward manifestations of the illness, coverage policies pertaining to annual renewal for existing and new PNH therapies should be designed to avoid unnecessary treatment disruptions, which patients and patient advocates expressed is an ongoing issue. Similarly, improvement in hematologic response, whether defined as hemoglobin level above a prespecified threshold or avoidance of red blood cell transfusions, should not trigger a denial of continued coverage, because withholding therapy will predictably result in hemolysis and potentially thrombosis.

Coverage Criteria: General

ICER has previously described general criteria for fair coverage policies that should be considered as cornerstones of any drug coverage policy: https://icer.org/wpcontent/uploads/2020/11/Cornerstones-of-Fair-Drug-Coverage-_-September-28-2020.pdf

Drug-Specific Considerations

Although PNH is a rare disease, the need for indefinite therapy to manage the illness and the high annual prices for existing and newer treatments, may lead payers to develop prior authorization criteria and to consider other limits on utilization.

None of these limits, however, should undermine the tenets of fair access to which all patients have a fundamental right. To explore the appropriate application of evidence to coverage policy, and to reflect the views of patient experts and clinicians on specific ways that payers might appropriately use coverage policy to manage resources prudently, we present the following perspectives on specific elements of cost sharing and coverage criteria for oral iptacopan and add-on danicopan.

Coverage Criteria for Iptacopan

- **Age:** Age criteria, if given, will likely follow the FDA label in line with clinical trial eligibility criteria. There are no ongoing clinical trials in pediatric populations. However, payers should have efficient mechanisms for clinicians to seek coverage exceptions for patients with serious unmet need who are near the cutoff for the age necessary for coverage.

- **Clinical eligibility**: If payers are considering establishing clinical eligibility criteria for coverage beyond that specified in the FDA label, they will look to any existing clinical guidelines and to the eligibility criteria for the pivotal trial(s). For treatments of PNH, however, there are no established clinical guidelines, and payers may find no benefit in strictly applying pivotal trial eligibility criteria since the inclusion criteria focus on laboratory markers of hemolysis with minor variations across trials that experts consider to be meaningless differences. Experts also advised that there is no clear consensus on how to operationalize a definition of "clinically significant" extravascular hemolysis. Experts largely recommend treatment for patients with symptomatic PNH or those without symptoms but have a sufficiently large PNH clone size (e.g. ≥50%), which indicates a greater risk for thrombosis and hemolytic anemia. The severity of PNH can vary substantially over time and, from a patient's perspective, can include a combination of fatigue, symptoms from smooth muscle dysfunction (i.e, abdominal pain), burden from red blood cell transfusions, and major adverse vascular events, such as thromboses. Clinical attestation alone may be sufficient to identify clinically eligible patients.

- **Exclusion criteria**: It is reasonable to exclude patients with bone marrow failure as determined by prior history or absolute reticulocyte counts since complement inhibitors would not be expected to improve anemia in these situations. However, payers may similarly find no benefit in strictly applying this criterion from clinical trials since there were minor variations in the reticulocyte count cutoff used as a proxy of bone marrow failure.

- **Provider restrictions**: Patients and clinical experts agreed that it is reasonable to restrict prescriptions to hematologists.

Coverage Criteria for Danicopan add-on – Assuming FDA Approval

- **Age:** Age criteria, if given, will likely follow the FDA label in line with clinical trial eligibility criteria. There are no ongoing clinical trials in pediatric populations. However, payers should have efficient mechanisms for clinicians to seek coverage exceptions for patients with serious unmet need who are near the cutoff for the age necessary for coverage.

- **Clinical eligibility**: Experts would consider adding on danicopan if patients developed cs-EVH despite a stable regimen of a C5 inhibitor (defined as at least 6 months in the ALPHA trial) to improve hemoglobin and quality of life and to decrease transfusion dependence. However, payers may find no benefit in strictly applying pivotal trial eligibility criteria since the inclusion criteria largely focus on laboratory markers of EVH with minor variations between trials for proximal complement inhibitors studied in this subpopulation without stipulating symptoms or transfusion dependence. Although it was not required for inclusion in the pivotal trial, payers might consider a history of red blood cell transfusion within the prior 6 months as a criterion of clinically significant EVH since all participants in the ALPHA trial had received at least one transfusion.

- **Exclusion criteria**: It is reasonable to consider bone marrow failure as an exclusion criterion since complement inhibitors would not be expected to improve anemia in this setting. However, payers may find no benefit in applying a single criterion used in pivotal trials, since there were minor variations in the reticulocyte count cutpoint used as a proxy of bone marrow failure.

- **Provider restrictions**: Patients and clinical experts agreed that it is reasonable to restrict prescriptions to hematologists.

Step Therapy

Payers should allow patients and clinicians to choose from multiple options until there is greater certainty about long-term safety, durability, and comparative effectiveness to inform practice.

The lack of evidence to distinguish overall clinical outcomes between iptacopan and C5 inhibitors, along with the lack of clinical characteristics or biomarkers to help predict response, raise the possibility that payers will consider step therapy through a preferred option for patients beginning treatment. However, for treatment-naïve patients, clinical experts and patients argued that C5 inhibitors are seen as frontline therapy, and active utilization management has been very limited for PNH. Clinical experts and patients emphasize the importance of maintaining the ability to tailor treatment options given the important trade-offs involved between selecting older, more proven IV options and newer oral options. Any approach to step therapy would also need to be sensitive to socio-economic elements that may create important benefits for certain patients to take one option or the other.

In regard to danicopan, for treatment-experienced PNH patients who develop cs-EVH on a stable C5 inihbitor regimen, clinical experts do not not know which patients could be safely switched to pegcetacoplan or iptacopan monotherapy versus which patients should add on danicopan to a C5 inhibitor to ensure durable control of the most severe disease manifestations from uncontrolled terminal complement activation. Danicopan will only be used as an add-on to C5 inhibitor treatment, so there is likely going to be no interest among payers in considering a step therapy approach that would force patients to switch from C5 treatment to pegcetacoplan or iptacopan as an alternative to adding danicopan. While patients may do fine switching to pegcetacoplan or iptacopan monotherapy, experts expressed uncertainty about which patients would require dual proximal and terminal complement inhibition to adequately control their illness. However, there is no doubt that adding danicopan to C5 inhibitor treatment would create a much more expensive regimen than monotherapy with pegcetacoplan or iptacoplan. Given the current state of the evidence, clinical experts felt it would be reasonable for payers to consider contacting clinicians requesting danicopan to ensure that they are aware of these other treatment options, particularly that of iptacoplan, which would allow patients to try an oral regimen. However, as noted earlier, active utilization management has been very limited for PNH, and clinical experts and patients emphasize the importance of maintaining the ability to tailor treatment options given the important trade-offs involved between selecting older, more proven IV options and newer oral options.

Manufacturers

Recommendation 1

Manufacturers should set prices that will foster affordability and good access for all patients by aligning prices with the patient-centered therapeutic value of their treatments. In the setting of these new interventions for PNH, while there is considerable hope associated with the promise of the therapies, there also remains substantial uncertainty regarding their longer-term safety and effectiveness. Manufacturer pricing should also be moderated to reflect the substantial uncertainty about these longer-term outcomes.

Drug prices that are set well beyond the cost-effective range cause not only financial toxicity for patients and families using the treatments, but also contribute to general health care cost growth that pushes families out of the insurance pool, and that causes others to ration their own care in ways that can be harmful.

Manufacturers should therefore price novel treatments in accordance with the demonstrated benefits to patients. In settings of substantial uncertainty and need for indefinite therapy in PNH, initial pricing should err on the side of being more affordable. This would allow more patients access, generating additional data on the real-world effectiveness and safety of novel treatments that could be used in future assessment updates. With accumulation of evidence of substantial benefit for patients with PNH, manufacturers should be allowed to increase pricing in accordance with benefit.

PNH treatments may also be used in other complement-mediated illnesses, such as atypical hemolytic uremic syndrome. As evidence accrues for other indications, the value of drugs should be considered across the entire portfolio of indications, and should not be priced for PNH in isolation.

Recommendation 2

Manufacturers who develop therapies for PNH as an add-on to one of their existing drugs on the market should consider reduced pricing for the add-on therapy to achieve fair value compared to monotherapy treatment options.

Because treatment for PNH is indefinite, manufacturers who develop add-on therapies for PNH should consider bundled pricing of both drugs until further evidence clarifies the value of dual therapy compared to monotherapy. This is especially pertinent to danicopan, since it is an add-on therapy to a C5 inhibitor which is very expensive and by itself not considered to be cost-effective without generic biosimilar medications available on the market.

Recommendation 3

Establish new or contribute to existing long-term registries that can be used to assess the benefits and harms of proximal complement inhibitors for the treatment of PNH.

Because the evidence based is comprised of small trials of short duration, concerns persist about uncommon but potentially serious risks of the proximal complement inhibitors, including breakthrough intravascular hemolysis and thrombosis. Whether these harms will manifest due to nonadherence or complement amplifying conditions (ie infections) require long-term follow-up studies that assess the durability of response and safety profiles. Registries would also enable comparative effectiveness research to identify the relative benefits and harms of pegcetacoplan, ipatcopan, and add-on danicopan versus C5 inhibitors alone, as well as compared to one another.

The absence of this evidence may otherwise limit uptake by patients and clinicians to these promising therapies.

Recommendation 4

Support the use of standard quality of life measures for future clinical trials and registries to more reliably demonstrate the value of newer promising therapies for PNH.

Fatigue, hemoglobin, and transfusion avoidance are important patient-centered outcomes. However, they are rarely translated into utility measures that can be incorporated into cost effectiveness analyses. Manufacturers can advance the ability of all stakeholders to understand the broader value of treatment by collecting and reporting commonly used quality of life measures in clinical trials and registries to better value newer promising treatments for PNH compared to existing therapies such as C5 inihibitors which have transformed the illness by controlling the most severe illness manifestations.

Clinicians and Clinical Societies

Recommendation 1

Track the horizon of important emerging therapies and be prepared to issue updated treatment guidelines for patients with PNH in a form that is easy to interpret and use by clinicians, patients, and payers

There are no official treatment guidelines for PNH. Before the availability of newer medications, current recommendations for C5 inhibitors and pegcetacoplan were guided by expert and consensus opinion. Clinical societies should issue an official practice guideline for managing patients with PNH to include newer therapies such as iptacopan and if approved, add-on danicopan. To an extent often not appreciated by clinicians, payers actively seek out authoritative clinical guidelines and use them as a foundation of prior authorization criteria. Ideally, guidelines should provide information on options to be used by clinicians and patients for shared decision making and offer pragmatic advice about how to select among different therapies for treatment-experienced PNH patients who develop cs-EVH.

Policymakers

Recommendation 1

The value of novel PNH therapies should not be determined exclusively by estimates of long-term cost offsets used in traditional cost-effectiveness analyses alone, particularly when the existing standard of care is acknowledged to be priced significantly higher than reasonable cost-effective levels.

New therapies that improve hemoglobin, fatigue, quality of life, transfusion dependence, and convenience through oral formulations offer the potential for significant value for patients. But that value must be tempered by the extremely high costs of the current standard of care, especially given that treatment is indefinite. When the costs of C5 inhibitors exceed levels that reflect the opportunity cost for new treatments in the health system, simply aggregating those costs over the lifetime of patients and assigning all potential cost offsets to the "value" of the new therapy, magnifies the existing distortion of value and pricing in the US health care system, denying the chance for the health system to recoup some of the cost savings so that innovation can be kept more affordable for all patients. Assigning the full cost offset to novel PNH therapies also creates a distortion in the incentives for innovation, skewing them strongly away from addressing conditions that are either fatal in the short term, such as genetic diseases of newborns, or that have few added health care costs, such as blindness.

Given these contextual factors, all stakeholders and policymakers should avoid using traditional cost-effectiveness analysis alone as a guide to considerations of fair pricing. Capping credit for cost offsets in some way should be explored further as an alternative approach to calculating ranges of fair pricing. This report provided an alternate way to "share savings" from new PNH treatments by offsetting the cost of C5 inhibitors, which substantially reduced the price estimate for iptacopan to achieve commonly acceptable thresholds compared to the traditional approach. This option and other ways to address these broader questions should be considered today to prepare for "fair pricing" of the innovative treatments of tomorrow.

Researchers/Regulators

Recommendation 1

Develop studies to evaluate the long-term durability, safety, and comparative effectiveness of different treatment options for PNH

In conjunction with manufacturers, payers, and patient organizations, researchers should prioritize collecting real-world data in the form of registries for clinical information combined with claims data for medication prescriptions to study the long-term durability of response, safety profiles, and comparative effectiveness of treatments for PNH to better inform practice guidelines. Regarding safety, a better understanding of the long-term risks is needed from nonadherence, which could be estimated using a medication possession ratio from claims data, and from different complement-amplifying conditions such as infections and surgery.

Recommendation 2

Develop prediction models and biomarkers to identify subpopulations of patients who may benefit from specific treatment strategies for PNH

A gap in the current management of patients with PNH shared by clinical experts was an inability to identify which patients are at risk for developing the most feared complications of PNH if treated with a proximal complement inihibitor alone—severe hemolytic anemia and thromboses. While clone size is the best deteriment of severity of illness, patients with the same clone size can have substantially different illness course. Thus, new biomarkers and/or the development of more accurate prediction models may better guide treatment selection upfront before complications develop.

Appendix

Appendix Tables 1 through I3 contain conflict of interest (COI) disclosures for all participants at the Friday, February 16, 2024 Public meeting of Iptacopan and Danicopan for Paroxysmal Nocturnal Hemoglobinuria.

Appendix Table 1. ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants*	
Foluso Agboola, MBBS, MPH, Vice President of Research, ICER	**Josh Carlson, PhD, MPH**, Professor, Department of Pharmacy, University of Washington
Sarah Emond, MPP, President and CEO, ICER	**Grace Ham, BS**, Program and Events Coordinator, ICER
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*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Appendix Table 2. CTAF Panel Member Participants and COI Disclosures

Participating Members of CTAF*	
Ralph Brindis, MD, MPH, MACC, FSCAI, FAHA, Clinical Professor of Medicine, UCSF	Felicia Cohn, PhD, HEC-C, Bioethics Director, Kaiser Permanente Orange County/ University of California Irvine School of Medicine
Robert Collyar, Patient Advocate, Breast Cancer; Board Member, Breast Cancer Action; Co-Founder, Clinical Trials Information Project	Rena Fox, MD, Professor of Medicine, UCSF
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Joanna Smith, LCSW, MPH, Healthcare Advocate	

*No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Appendix Table 3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Leigh Clark, BCPA, Director, Patient Services, Aplastic Anemia and MDS International Foundation	AAMDSIF has received <25% of funding from healthcare companies.
Eve Hindin, PharmD, MS, Executive Director, Clinical Formulary, CVS Health	Dr. Hindin is a full-time employee at CVS Health.
Jeri Keiller, Certified Public Accountant	No conflicts to disclose.
Irina Murakhovskaya, MD, Associate Professor, Albert Einstein College of Medicine and Montefiore Medical Center	Dr. Murakhovskaya has received more than $5,000 in honoraria or consulting fees from Novartis and Alexion. Dr. Murakhovskaya has also received >25% of

	funding from WAIHA Warriors and has served as the Principal Investigator for the Novartis CLNP023C12303 trial.
Caroline Piatek, MD, Associate Professor of Clinical Medicine, University of Southern California	Dr. Piatek has received more than $5,000 in honoraria or consulting fees from Argenx, Omeros, Janssen, Novartis, AstraZeneca/Alexion, Rigel, Apellis, Sanofi, Sobi. Dr. Piatek has also received manufacturer support through AstraZeneca/Alexion, Apellis.
Emily Tsiao, PharmD, BCPS, Clinical Pharmacist of Medical Policies, Premera	Dr. Tsiao is a full-time employee at Premera.