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Iptacopan and danicopan for paroxysmal nocturnal hemoglobinuria

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Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired blood disorder characterized by hemolytic anemia and thrombosis.[1] Hemolytic anemia predominantly presents as fatigue, with severe cases requiring continued dependence on blood transfusion. Thrombosis occurs in about 30% of PNH cases and is the leading cause of death among patients with PNH.[2,3] PNH affects a minute fraction of the population, with an estimated incidence of 1 to 2 persons per million per year and a prevalence ranging from 10 to 20 per million.[4,5] This disease primarily manifests in adults with a median age of onset in their 30s without any association with demographic factors, including sex, race and ethnicity, or geography.[6]

The introduction of C5 inhibitors (eculizumab and ravulizumab) has led to a significant transformation in the management of PNH, notably by greatly reducing intravascular hemolysis (IVH), thrombosis, and death. Hence, patients with PNH now have life expectancies similar to those of age-matched individuals without PNH.[7-9] Ravulizumab is often favored more than eculizumab because of its prolonged half-life with lower breakthrough IVH.[10] Despite the efficacy of C5 inhibitors, around one-third of treated patients with PNH still have symptomatic anemia, and 20% remain transfusion-dependent, which is in part because of clinically significant extravascular hemolysis (cs-EVH) that is amplified by the mechanistic consequence of C5 inhibition.[11]

Proximal complement inhibitors are a new class of drugs that have emerged as potential solutions for addressing the current limitations of C5 inhibitors with cs-EVH. Pegcetacoplan, which is subcutaneously administered twice weekly, was the first to be approved in this class for all patients with PNH. More recently, 2 new proximal complement inhibitors that may influence treatment decisions for patients with PNH have been approved. Iptacopan, an oral factor B inhibitor taken twice daily for the treatment of all patients with PNH, was approved by the US Food and Drug Administration (FDA) on December 6, 2023. Danicopan, an oral factor D inhibitor taken thrice daily, was approved by the FDA on April 1, 2024, as an add-on therapy to a C5 inhibitor for only treatment-experienced patients with cs-EVH.

The Institute for Clinical and Economic Review (ICER) conducted a systematic literature review and cost-effectiveness analysis to evaluate the clinical and economic outcomes of the newer agents, iptacopan and danicopan, for patients with PNH. This report presents a summary of our findings and highlights the key policy recommendations discussed at the California Technology Assessment Forum (CTAF) public meeting on February 16, 2024. The full report is available at: https://icer.org/wp-content/uploads/2024/03/PNH_Final-Report_For-Publication_03132024.pdf.

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Summary of Findings

CLINICAL EFFECTIVENESS

We did not attempt to compare iptacopan and danicopan with each other because of key differences in the trials. Instead, we evaluated each drug separately.

Iptacopan. Iptacopan was evaluated in 2 phase 3 trials. The first trial (APPOINT-PNH) was a single-arm, open-label trial that evaluated iptacopan as a first-line treatment in 40 patients with PNH naive to C5 inhibitors. Key inclusion criteria included a confirmed diagnosis of PNH with a clone size of at least 10%, hemoglobin levels of less than 10 g/dL, and a lactate dehydrogenase (LDH) of more than 1.5 times the upper limit of normal. Patients with PNH experienced with complement inhibitors (ie, eculizumab and ravulizumab) were excluded from this trial.[12] The primary endpoint of hematological response, which was defined as an increase of at least 2 g/dL in hemoglobin from baseline without transfusions, was achieved by 94% of the evaluable patients (n = 33) at week 24. LDH levels, a biomarker for IVH, decreased from baseline to less than or equal to 1.5 times the upper limit of normal levels in almost all patients (95%). In addition, there was a clinically meaningful improvement in fatigue with iptacopan.[13]

The second trial (APPLY-PNH) was a randomized, open-label trial that evaluated iptacopan as a second-line treatment in treatment-experienced patients with PNH on a stable C5 inhibitor with cs-EVH. Participants were randomized to switch to iptacopan (n = 62) or continue a C5 inhibitor (n = 35). The trial included patients with a documented diagnosis of PNH with a clone size of at least 10%, hemoglobin of less than 10g/dL, absolute reticulocyte counts greater than 100×10^9 cells/L, who were currently on a stable regimen of eculizumab or ravulizumab for at least 6 months prior to randomization. Key exclusion criteria included bone marrow failure, hematopoietic stem cell transplant, or known or suspected hereditary complement deficiency.[14] At week 24, the majority of patients on iptacopan achieved the coprimary endpoint of at least 2 g/dL improvement in hemoglobin from baseline (85% of patients) and sustained hemoglobin levels of at least 12 g/dL without transfusions (70% of patients). In contrast, none of the patients in the C5 inhibitor arm achieved either endpoint. Similarly, iptacopan demonstrated a statistically significant and clinically meaningful improvement in fatigue from baseline compared with the C5 inhibitor arm (treatment difference: +8.3 points; $P < 0.001$). However, there was no statistically significant difference between the 2 arms in lowering LDH, suggesting comparable efficacy in controlling IVH.[15]

The most frequent adverse events with iptacopan were headache and diarrhea. A lower rate of breakthrough hemolysis was observed in the iptacopan arm compared with the C5 inhibitor arm. There were no deaths or discontinuations because of adverse events or breakthrough hemolysis in either trial.[13,15] However, there was 1 death during the extension trial from an encapsulated bacterial infection.[16] Iptacopan carries a black box warning for serious infection caused by encapsulated infection.

Danicopan. Evidence on danicopan was derived from a phase 3, randomized, placebo-controlled trial (ALPHA). The trial evaluated danicopan as an add-on therapy to a C5 inhibitor (danicopan plus C5 inhibitor, n = 57) continuing C5 inhibitor alone (placebo plus C5 inhibitor, n = 29) in treatment-experienced PNH with cs-EVH. The trial enrolled patients who had been on a C5 inhibitor for at least 6 months and had EVH as indicated by hemoglobin levels less than or equal to 9.5 g/dL and absolute reticulocyte count of at least 120×10^9/L. Participants with a history of bone marrow failure, hematopoietic stem cell transplantation, or hereditary complement deficiency were excluded from the trial.[17] The primary endpoint of change from baseline in hemoglobin levels at week 12 favored the danicopan arm (2.9 g/dL vs 0.5 g/dL; treatment difference: +2.4 g/dL, $P < 0.0001$). Both arms maintained near-normal LDH levels. In addition, danicopan led to a statistically significant and clinically meaningful improvement in fatigue vs the add-on placebo group (treatment difference: +6.1 points; $P = 0.002$).[18]

The most frequent adverse events in the ALPHA trial were headache, liver enzyme elevation, nausea, diarrhea, and arthralgia, with rates being slightly higher in the danicopan add-on arm. Four participants receiving danicopan experienced breakthrough hemolysis during the trial. There were no deaths or discontinuations because of breakthrough hemolysis.[17] However, 3 participants discontinued treatment because of other treatment-related adverse events.[19]

UNCERTAINTIES BECAUSE OF LIMITATIONS IN THE CLINICAL EVIDENCE

The main source of uncertainty for both iptacopan and danicopan arises from small and short-term clinical trials conducted mostly in countries outside of the United States, where standards of care may differ. Hence, the generalizability, durability of findings, and safety profiles of both these proximal complement inhibitors are uncertain. For iptacopan monotherapy, clinical experts were most concerned about risks of breakthrough hemolysis and thrombosis in settings with lower adherence rates and greater complement-amplifying conditions such as infections or major surgeries, which can overwhelm the proximal complement inhibition. However, for danicopan, the addition of a C5 inhibitor obviates these concerns. Finally, we have no direct comparative evidence to evaluate iptacopan vs C5 inhibitor, the standard of care, as frontline therapy for treatment-naive patients with PNH or either intervention vs pegcetacoplan (the first proximal complement inhibitor) for treatment-experienced patients with cs-EVH.

TABLE 1 Base-Case Results and Incremental Cost-Effectiveness Ratios for Iptacopan Compared With Ravulizumab, Health Care Sector Perspective

Intervention	Drug cost	Total cost	QALYs	evLYs	LYs	Cost per QALY gained	Cost per evLY gained
Iptacopan	$2,360,000	$2,375,000	3.65	3.65	4.29	$1,368,000	$1,368,000
Ravulizumab	$2,088,000	$2,175,000	3.50	3.50	4.29	Reference	Reference

Cost per LYs gained was not calculable because of assumed equivalence in LYs (difference of <0.01).
evLY = equal value of life-year; LY = life-year; QALY = quality-adjusted life-year.

TABLE 2 Base-Case Results and Incremental Cost-Effectiveness Ratios for Danicopan Add-On Therapy Compared With Ravulizumab Alone, Health Care Sector Perspective

Intervention	Drug cost	Total cost	QALYs	evLYs	LYs	Cost per QALY gained	Cost per evLY gained
Danicopan add-on to ravulizumab	$2,712,000[a]	$2,737,000[a]	3.51	3.51	4.26	$9,457,000[a]	$9,457,000[a]
Ravulizumab alone	$2,073,000	$2,144,000	3.45	3.45	4.26	Reference	Reference

Cost per LYs gained was not calculable because of equivalence in LYs.
[a]Based on danicopan placeholder price.
evLY = equal value of life-year; LY = life-year; QALY = quality-adjusted life-year.

LONG-TERM COST-EFFECTIVENESS

A de novo decision analytic model was used to estimate the cost-effectiveness of iptacopan and add-on danicopan for treatment-experienced patients with PNH with clinically significant EVH from a US health care sector perspective. Each intervention, iptacopan, and add-on danicopan was evaluated separately against ravulizumab alone, using data from APPLY-PNH and ALPHA clinical trials, respectively. We used a Markov model with a cycle length of 24 weeks, a 5-year time horizon, and 4 health states: 2 for transfusion avoidant differentiated as "hemoglobin normalized" and "hemoglobin not normalized," 1 for transfusion-dependent, and death. The model inputs were derived from key clinical trials of interventions and comparators, manufacturer-submitted data, publicly available literature, and prior economic models. Further details about the model and key assumptions can be found in the full report: https://icer.org/wp-content/uploads/2024/03/PNH_Final-Report_For-Publication_03132024.pdf.

The economic model found that at the annual price of $550,377, treatment with iptacopan resulted in incremental cost-effectiveness ratios that exceeded the commonly accepted thresholds (Table 1). In estimating the ICER health-benefit price benchmarks (HBPBs), we adopted an alternative methodology in which cost offsets are not fully assigned to the manufacturer. We argue that this is the more policy-relevant approach in situations in which a large percentage of the traditional HBPB comes from the cost offset of therapies, such as C5 inhibitors that themselves have prices that are not believed to be aligned with benefits to patients. In this case, we found that 97% of the HBPB was because of offsetting the cost of C5 inhibitors ravulizumab. Therefore, we calculated the HBPB using a $150,000 annual cap on offsets as described in our value assessment framework. Using this alternative method, we calculated the HBPB for iptacopan to range between $178,000 and $180,000 annually.

For danicopan, the manufacturer had not yet announced a price at the time of our review. Based on analyst estimates, we used a placeholder price of $150,000 annually for danicopan in the model. At this placeholder price, the incremental cost-effectiveness ratios for danicopan exceeded the commonly accepted thresholds (Table 2). The ICER calculated HBPBs for danicopan, which was not subject to any shared savings scenario (because it is an add-on therapy to C5 and not a replacement), is an annual price of $12,300 to $13,100.

LIMITATIONS OF THE COST-EFFECTIVENESS MODEL

Both therapies were evaluated in small, short-term trials. As such, we had to extrapolate the 24-week initial health state to a 5-year time horizon. Studies with longer follow-up periods would better inform our model parameters. In addition, C5 inhibitors, the current standard of care, are highly costly at approximately $450,000 to $500,000 per year and have not been shown to meet common cost-effectiveness thresholds. Using the traditional

TABLE 3 California Technology Assessment Forum Votes on Contextual Considerations

Contextual consideration	Very low priority	Low priority	Average priority	High priority	Very high priority
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability	0	5	6	2	0
Magnitude of the lifetime impact on individual patients of the condition being treated	0	0	6	7	0

cost-effectiveness approach, any incremental gains for new PNH therapies, like iptacopan, would lead to an even higher value-based price. This creates tension about the extent to which the high cost of C5 inhibitors should drive consideration for the pricing of new PNH therapies. We addressed this concern using an alternate methodology, a shared savings scenario with a $150,000 annual cap on cost offsets to estimate what we feel is the most fair pricing for iptacopan.[20]

Policy Discussion

The CTAF is one of the independent appraisal committees including multiple stakeholders (ie, clinicians, methodologists, and patient advocates) convened by ICER to engage in the public deliberation of the evidence on clinical and cost-effectiveness of health care interventions. The ICER report on iptacopan and danicopan for PNH was the subject of a CTAF meeting on February 16, 2024. Following the discussion, the CTAF panel members deliberated on key questions raised by ICER's report.

The results of their votes on the clinical evidence are as follows: (1) The panel voted 12-1 that the evidence is not adequate to demonstrate that the net health benefit of iptacopan is superior to that provided by C5 inhibitors therapies in treatment-naive patients with PNH; 2) the panel voted 7-6 that the evidence is not adequate to demonstrate that the net health benefit of iptacopan is superior to continuing C5 inhibitor therapy in treatment-experienced patients with PNH on a stable C5 inhibitor regimen with cs-EVH; and 3) the panel voted 10-3 that current evidence is adequate to demonstrate that the net health benefit of adding danicopan to a C5-inhibitor is superior to that provided by continuing C5 inhibitor alone in treatment-experienced patients with PNH on a stable C5 inhibitor regimen with cs-EVH.

The CTAF also voted on "contextual considerations" and "potential other benefits" as part of a process intended to signal to policymakers whether there are important considerations when making judgments about long-term value for money not fully represented in analyses of clinical and/or cost-effectiveness. The results of these votes are presented in Tables 3 and 4. The final votes on the long-term value for money reflect the integration of the contextual considerations, other potential benefits, and the cost-effectiveness results. The majority of the panel (12 out of 13) voted that iptacopan, at its current price of about $550,377, provides a "low" long-term value for money (Table 5). The long-term value for money vote for danicopan was not taken at the public meeting because the manufacturer had not yet announced a price.

Following the discussion of the evidence, a policy roundtable was convened to deliberate on how best to translate the evidence and additional considerations into clinical practice, pricing, and insurance coverage policies. The full set of policy recommendations can be found here: https://icer.org/wp-content/uploads/2024/03/PNH_Policy_Recommendations_03132024.pdf.

KEY POLICY RECOMMENDATIONS INCLUDE:

- Payers should be aware of several key issues regarding the treatment landscape for PNH
  - Patients and clinicians have become accustomed to and expressed satisfaction with the use of intravenously administered C5 inhibitors as frontline therapy for treatment-naive patients
  - Clinicians lack prediction models or biomarkers to identify patients treated with a C5 inhibitor who may develop cs-EVH or to determine the best second-line treatment strategy
  - There is a high value placed on individualized shared decision-making for patients when choosing between a C5 inhibitor and nonintravenous treatment options.
- Out-of-pocket costs and access are a concern, given the need for indefinite treatment and the high costs of PNH therapies. Payers should ensure equitable out-of-pocket cost burden under the pharmaceutical benefit for newer oral therapies compared with existing C5 inhibitor infusions covered under the medical benefit.
- Annual coverage renewal requirements for therapies targeting PNH should either be eliminated or implemented

TABLE 4 California Technology Assessment Forum Votes on Potential Other Benefits or Disadvantages Questions

Potential other benefit or disadvantage	Major negative effect	Minor negative effect	No difference	Minor positive effect	Major positive effect
What are the relative effects of switching to iptacopan vs continuing C5 inhibitors on the following outcomes that inform judgment of the overall long-term value for money of iptacopan?					
Patients' ability to achieve major life goals related to education, work, or family life	0	0	0	8	5
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	0	0	3	9	1
Patients' ability to manage and sustain treatment given the complexity of regimen	1	0	2	7	3
Society's goal of reducing health inequities	1	2	8	2	0
What are the relative effects of adding danicopan to C5 inhibitors vs C5 inhibitors alone on the following outcomes that inform judgment of the overall long-term value for money of danicopan?					
Patients' ability to achieve major life goals related to education, work, or family life	0	0	3	9	1
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	0	0	7	6	0
Patients' ability to manage and sustain treatment given the complexity of regimen	1	7	2	3	0
Society's goal of reducing health inequities	2	2	9	0	0

TABLE 5 California Technology Assessment Forum Votes on Long-Term Value for Money at Current Prices for Iptacopan

Question	Low long-term value for money at current pricing	Intermediate long-term value for money at current pricing	High long-term value for money at current pricing
Given the available evidence on comparative effectiveness, incremental cost-effectiveness, and potential other benefits or disadvantages, what is the long-term value for money of treatment at current pricing with iptacopan vs C5 inhibitors?	12	1	0

through a separate time-sensitive process to prevent missing doses and should not penalize patients for improvement on therapy as a reason for denial of continued coverage.

- Manufacturers developing therapies for PNH as an add-on to their existing drugs on the market should consider offering reduced pricing for the add-on therapy to ensure fair value compared with monotherapy treatment options.

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