REPORT AT A GLANCE:
PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

MARCH 2024

Key Findings

Population	Treatment	Comparator	Evidence Rating	Annual WAC	Health-Benefit Price Benchmark
Treatment-Naïve to Complement Inhibitors	Iptacopan	C5 inhibitor	Insufficient ("I")	--	--
Treatment-Experienced on a Stable C5 Inhibitor Regimen with Clinically Significant EVH	Iptacopan	C5 inhibitor	Promising but inconclusive (P/I)	$550,377 per year	$178,000 to $180,000 per year
	Iptacopan	Pegcetacoplan	Insufficient ("I")	--	--
	Danicopan + C5 Inhibitors	C5 inhibitor	Comparable or better (C++)	Placeholder price: $150,000 per year	$12,300 to $13,100 per year
	Danicopan + C5 Inhibitors	Pegcetacoplan	Insufficient ("I")	--	--

"PNH is a rare, acquired blood disorder that primarily manifests in fatigue, and if severe, requires lifelong dependence on blood transfusions. Iptacopan (as an alternative to C5 inhibitor therapy) and danicopan (as an add-on to a C5 inhibitor) are promising new oral options for PNH patients. As indicated by the votes from the independent appraisal committee, the current evidence was judged more favorably for add-on danicopan in treatment-experienced PNH patients with anemia; however, there are still uncertainties around the long-term benefits of both therapies. The discussion during the public meeting highlighted the impact of high costs associated with C5 inhibitors - the current standard of care for PNH - on accessibility and affordability, and its effect on the pricing of new PNH therapies."

– ICER's Vice President of Research Foluso Agboola, MBBS, MPH

Key Findings

THEMES AND RECOMMENDATIONS

- 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 to existing C5 inhibitor infusions covered under the medical benefit. Payers should also eliminate annual coverage renewal requirements or implement this policy using a separate time-sensitive pathway to avoid missed doses.
- Given great uncertainty about the longer term safety and efficacy for newer treatment options, payers should be aware that clinicians and patients place a high value on shared decision making to choose between a C5 inhibitor and non-intravenous proximal complement inhibitor treatment options. To help fill these knowledge gaps, clinical societies should issue a treatment guideline to offer pragmatic advice about how to select among different therapies, and all stakeholders should contribute to registries to establish long-term safety and durability of newer treatments, and to enable comparative effectiveness research of different treatment strategies.
- 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 since the existing standard of care, C5 inhibitors, are priced significantly higher than cost-effective levels.

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired blood disorder characterized by chronic destruction of red blood cells (hemolytic anemia) and blood clots (thrombosis). Hemolytic anemia primarily manifests in fatigue, and if severe, requires lifelong dependence on blood transfusions. Thrombosis is the most common cause of death. The prevalence of PNH is 10 to 20 per million. PNH is primarily a disease of adults, without an association by sex, race, ethnicity, or geography.

PNH is caused by uncontrolled activation of the complement pathway of the immune system which causes hemolysis. C5 inhibitor therapy has transformed the disease by greatly reducing intravascular hemolysis (occurring within blood vessels), thrombosis, and death, with life expectancies similar to age-matched controls. An FDA-approved intravenous C5 inhibitor (eculizumab infusions every 2 weeks or ravulizumab infusions every 8 weeks) is recommended by clinical experts for the treatment of symptomatic PNH, which comprise up to two-thirds of PNH patients. Ravulizumab is preferred over eculizumab because of the fourfold longer half-life with less breakthrough hemolysis and lower costs. However, even with therapy, about 20% are transfusion-dependent because extravascular hemolysis (EVH) is a mechanistic consequent of C5 inhibitor therapy. Pegcetacoplan, a proximal complement inhibitor administered subcutaneously twice weekly, is another FDA-approved treatment option for PNH. Unlike C5 inhibitors, pegcetacoplan

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prevents both intra and extravascular hemolysis. However, clinical experts largely use pegcetacoplan only for patients on a stable C5 inhibitor regimen who have clinically significant EVH given their concern for its greater risk of breakthrough intravascular hemolysis and potentially thrombosis.

There are two first-in-class proximal complement inhibitors, iptacopan and danicopan. Iptacopan, an oral Factor B inhibitor taken twice daily, was approved by the FDA on December 6, 2023, for the treatment of all PNH patients. Danicopan, an oral Factor D inhibitor taken thrice daily, is being considered by the FDA for add-on therapy to a C5 inhibitor for only treatment-experienced patients on a stable C5 inhibitor regimen with clinically significant EVH.

Iptacopan was evaluated in two small 24-week trials. APPOINT-PNH, a single-arm trial of 40 treatment-naïve patients, found that most achieved substantial hematologic response (improved hemoglobin, transfusion avoidance, and fatigue). APPLY-PNH, an open-label RCT of 97 treatment-experienced patients with clinically significant EVH, similarly found improved hematologic response versus continuing a C5 inhibitor. Iptacopan achieved both co-primary endpoints of increased hemoglobin g/dL from baseline (85% vs 0%) and level ≥12 g/dL (70% vs 0%) without transfusions. In the APPLY-PNH trial, patients receiving iptacopan had few serious harms; 3.2% had breakthrough hemolysis and 1.6% had a thrombosis (versus 0% with thrombosis in the C5 inhibitor arm).

The evidence base for the efficacy of add-on danicopan was derived from the ALPHA trial, a 12-week placebo-controlled RCT of 86 treatment-experienced patients with clinically significant EVH. At the time of the publication of this report, we have data only on approximately the first 75% of the randomized population (n=63). Add-on danicopan substantially improved hematologic response versus add-on placebo, including the primary endpoint of change in hemoglobin from baseline between groups (+2.4 g/dL, p<0.001), and secondary outcomes of increased hemoglobin ≥2 g/dL from baseline without transfusions (60% versus 0%) and less fatigue. Danicopan had few serious harms.

Because of differences in treatment options and trial designs, we rated the clinical evidence separately for treatment-naive and treatment-experienced PNH populations.

For iptacopan, the two small studies of short duration did not assuage experts' concerns about the risk of breakthrough intravascular hemolysis and thrombosis. For treatment-naive PNH patients, we rate the evidence for iptacopan as insufficient ("I") given the lack of comparative efficacy data versus a C5 inhibitor, the consensus standard of care. For treatment-experienced PNH patients on a stable C5 inhibitor with clinically significant EVH, we rate the evidence for iptacopan versus continuing a C5 inhibitor as promising for moderate to substantial net benefit but inconclusive ("P/I") because of the uncertainty about the long-term benefit and safety, particularly related to breakthrough hemolysis and the more consequential but less common complication of thrombosis. Additionally, while recognizing it's a more convenient oral formulation, given the lack of comparative efficacy data to pegcetacoplan, we rate the evidence for iptacopan versus pegcetacoplan as insufficient ("I").

For add-on danicopan to a C5 inhibitor, patients and clinicians welcomed the dual protection against both intra and extravascular hemolysis plus the greater certainty of protection against thrombosis, although were concerned about the costs. Although the trial was small and of short duration, because it was well tolerated and combined with C5 inhibition, we rate danicopan added on to a C5 inhibitor for treatment-experienced PNH patients with clinically significant EVH as comparable or better than

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continuing a C5 inhibitor (C++). However, given the lack of comparative efficacy data, we rate the evidence of add-on danicopan to a C5 inhibitor versus pegcetacoplan as insufficient ("I").

Economic Analyses

LONG-TERM COST EFFECTIVENESS

We developed a de novo decision analytic model to estimate the cost-effectiveness of iptacopan versus ravulizumab and add-on danicopan versus ravulizumab alone in treatment-experienced patients with PNH with clinically significant extravascular hemolysis from a health care perspective.

Compared with ravulizumab, treatment with iptacopan resulted in small gains in QALYs and evLYs and equivalent LYs. At the annual placeholder price of $550,377 treatment with iptacopan would cost more than ravulizumab, resulting in an estimated incremental cost-effectiveness ratio of $1,368,000 per QALY or evLY gained. As discussed in greater detail in Section 6, ICER has concluded that in a situation where a large percentage of the traditional Health Benefit Price Benchmark (HBPB) comes from cost offsets of therapies that, themselves, have prices that are not believed to be aligned with benefits to patients, ICER will present ranges from shared savings calculations as the most appropriated HBPBs. We calculate that approximately 97% of the traditional HBPB for iptacopan come from offsetting the cost of C5 inhibitor therapies that, themselves, have prices that are not believed to be aligned with benefits to patients. Under the shared saving scenario with a $150,000 annual cap on cost offsets, the HBPB for iptacopan is $178,000 to $180,000 annually.

In the comparison of add-on danicopan to ravulizumab alone, treatment with add-on danicopan resulted in small gains in QALYs and evLYs and the same number of LYs. Using the annual placeholder price of $150,000, treatment with add-on danicopan resulted in substantially more costs. At the assumed placeholder price, the incremental cost-effectiveness ratio for add-on danicopan is $9,457,000 per QALY or evLY gained. The HBPB for danicopan used as add-on therapy to a C5 inhibitor, is an annual price of $12,300 to $13,100.

POTENTIAL BUDGET IMPACT

Results showed that at the current annual WAC price for iptacopan ($550,377) and the placeholder price for danicopan ($150,000 annually), all patients (N=55 patients per year) could be treated over the span of five years without crossing the ICER budget impact threshold of $735 million per year.

Public Meeting Deliberations

VOTING RESULTS

ICER assessed, and the independent appraisal committee voted on, the evidence of iptacopan for individuals with treatment-naïve PNH:

- A majority of panelists (12-1) found that current evidence is **not adequate** to demonstrate a net health benefit for iptacopan when compared to C5 inhibitor therapies.

For treatment-experienced individuals on a stable C5 Inhibitor regimen with clinically significant extravascular hemolysis:

- A slight majority of panelists (7-6) found that current evidence is **not adequate** to demonstrate a net health benefit for switching to iptacopan when compared to continuing a C5 inhibitor.
- A majority of panelists (12-1) found that current evidence is **not adequate** to demonstrate a net health benefit for switching to iptacopan when compared to continuing pegcetacoplan.
- A majority of panelists (10-3) found that current evidence is **adequate** to demonstrate a net health benefit for adding danicopan to a C5 inhibitor when compared to a C5 inhibitor alone.
- All panelists (13-0) found that current evidence is **not adequate** to demonstrate a net health benefit for adding danicopan to a C5 inhibitor when compared to pegcetacoplan alone.

Panel members also weighed potential benefits and disadvantages beyond the direct health effects and broader contextual considerations. Voting highlighted the following as particularly important for payers and other policymakers to note:

- Magnitude of the lifetime impact on individual patients of PNH;
- Patients' ability to achieve major life goals related to education, work, or family life;
- Patients' ability to manage and sustain treatment given the complexity of regimen.

After reviewing the clinical evidence and considering the treatments' other potential benefits, disadvantages, and contextual considerations noted above, the CTAF evaluated the long-term value of iptacopan at its current pricing:

- A majority of panelists (12-1) found that iptacopan at its current pricing represents **"low"** long-term value for money.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

For more information about ICER, please visit ICER's website (www.icer.org).