Iptacopan and Danicopan for Paroxysmal Nocturnal Hemoglobinuria

Revised Background and Scope

August 22, 2023

Background

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired blood disorder characterized by chronic destruction of red blood cells (hemolytic anemia) and blood clots (thrombosis).[1] Hemolytic anemia primarily manifests in fatigue, and if severe, requires lifelong dependence on blood transfusions. Thrombosis is the most common cause of death in patients with PNH.[2,3]

PNH affects one to two persons per million with a prevalence ranging from 10 to 20 per million.[4,5] PNH is primarily a disease of adults, with a median age of onset in the 30s, without an association by sex, race, ethnicity, or geography.[6]

PNH is caused by the deficiency of two proteins, CD55 and CD59, on the surface of precursor red blood cells in the bone marrow, which prevent destruction by a part of the immune system known as the complement pathway (**Figure 1**).[7] The deficiency of CD59 leads to intravascular hemolysis (occurring within blood vessels) by uncontrolled C5 activation in the terminal complement pathway, and accounts for most PNH manifestations. CD55 deficiency leads to extravascular hemolysis in organs like the spleen by uncontrolled C3 activation in the proximal complement pathway.

The introduction of the C5 inhibitor eculizumab in 2008, followed by ravulizumab in 2018, has transformed the disease by greatly reducing intravascular hemolysis, thrombosis, and death, with life expectancies similar to age-matched controls.[8-10] Because PNH is a chronic disease and C5 inhibitors are costly (about $500,000/year),[11] the lifelong costs of treatment are over $9 million dollars.[12]

Even with C5 inhibitor therapy, about one-third of patients have symptomatic anemia; and up to 20% are transfusion-dependent.[13] One major reason for this is because C5 inhibitors increase extravascular hemolysis due to uncontrolled C3 activation. Another major reason for persistent anemia is bone marrow failure, which is unrelated to complement activation.[14]

PNH is a clinical diagnosis confirmed by a peripheral flow cytometry blood test which counts the clone size—the number of cells that are affected by PNH. Clone size is the main determinant of severity—the greater the size the greater the hemolysis.[15] Clone size tends to be either very low or

very high, with clinically significant hemolysis typically beginning at sizes greater than 50%.[15,16] Patients with PNH should also undergo a bone marrow biopsy to exclude bone marrow failure, namely aplastic anemia, which is the only known risk factor for PNH.

PNH is classified into three categories: subclinical PNH, PNH with bone marrow failure, and classic PNH. The former two categories tend to have small clone sizes, and as such are asymptomatic or have modest symptoms. Classic PNH has very large clone sizes with considerable hemolysis and thrombosis risk.

There are currently no clinical guidelines for PNH. Consensus statements recommend an intravenous anti-C5 monoclonal antibody approved by the Food and Drug Administration (FDA) for the treatment of symptomatic PNH, which comprise up to two-thirds of PNH patients.[4,6,10,15,17] Ravulizumab is preferred over eculizumab because of the fourfold longer half-life (dosed every eight vs. two weeks) with less breakthrough hemolysis and lower costs.[12,18] Pegcetacoplan, a peptide administered subcutaneously twice weekly that inhibits C3, is another FDA-approved treatment option for patient with PNH. Pegcetacoplan may have increased incidence and severity of breakthrough hemolysis versus C5 inhibitors due to its shorter half-life and its mechanism of action with the potential amplification effect of C3b on C5 activation (**Figure 1**).[13,19]

Figure 1. Drugs Targeting The Complement Pathway
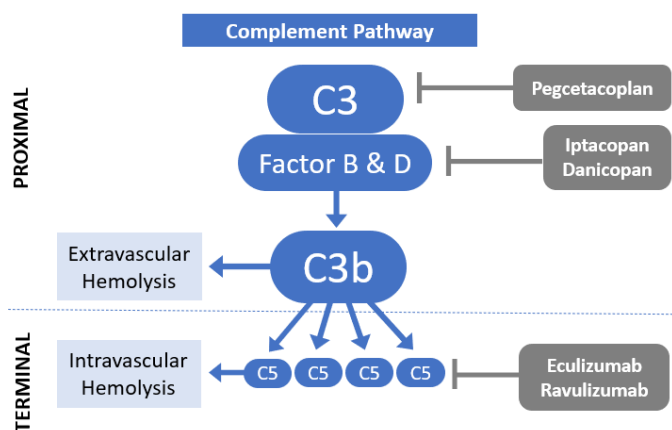
In addition to complement inhibition, patients should also receive supportive care, including blood transfusions for symptomatic anemia, iron and vitamin supplementation, blood thinners for thromboses, and possibly short-courses of corticosteroids for hemolytic episodes.[4,10,17] Bone marrow transplant is the only cure for PNH, but because of its considerable morbidity and mortality, it is largely only recommended for patients with severe bone marrow failure.

In addition to the complement inhibitors already FDA-approved, there are additional agents in development, including two proximal complement inhibitors, Iptacopan and Danicopan. Iptacopan, an oral Factor B inhibitor taken twice daily, is being considered for the treatment of all PNH patients. Danicopan, an oral Factor D inhibitor taken thrice daily, is being considered for add-on therapy to a C5 inhibitor for patients with clinically significant extravascular hemolysis. Given these potential different options, there is a need to understand the comparative benefits and costs of the treatments for PNH.

Stakeholder Input

This draft scoping document was developed with input from diverse stakeholders, including patient advocacy groups, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

Patients with PNH often experience a long and frustrating path to diagnosis due to its rarity and the nature of its diverse symptoms. Patient advocacy groups emphasized that PNH is a chronic illness that requires lifelong treatment. Patients are most concerned with fatigue, quality of life, treatment burden, and costs of therapy. Since younger adults are often affected, adapting treatment to fit patients' daily routines is an important consideration for adherence and convenience. Another treatment consideration for women of childbearing age is fertility, where eculizumab is the drug of choice, given established safety information regarding use in pregnancy.

We heard from all stakeholders that C5 inhibitors have significantly reduced the burden of PNH and thus have become the standard of care for PNH; however, some patients still experience extravascular hemolysis and anemia, requiring blood transfusions while on treatment. Clinical experts welcomed new treatment options but emphasized the importance of convenience, compliance, and cost. Dosing frequency, mode of administration, and site of administration are major considerations for patients. One overarching theme we heard from clinical experts is the importance of understanding the potential risks for breakthrough hemolysis with new treatment options that target the proximal complement pathway. Finally, we heard the cost of current treatments is substantial and estimated to cost approximately $500,000 annually.

Report Aim

This project will evaluate the health and economic outcomes of Iptacopan and Danicopan for paroxysmal nocturnal hemoglobinuria. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Applicable Framework Adaptations

We propose to assess Iptacopan and Danicopan under an adaptation of the [ICER Value Framework for treatments of serious, ultra-rare conditions](#) because we believe they meet the following criteria:

The eligible patient populations for the treatment indication(s) included in the scope of the ICER review is estimated at fewer than approximately 10,000 individuals. There are no ongoing or planned clinical trials of the treatment for a patient population greater than approximately 10,000 individuals.

Following formal public comment and discussions with stakeholders, ICER will make a final decision on whether the therapy meets these criteria and will be assessed using an adapted approach.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; comparative cohort studies and case reports will also be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

The population of focus for the review is patients with PNH. Subpopulations of interest include treatment-naïve PNH and treated PNH with clinically significant extravascular hemolysis.

Interventions

The full list of interventions of interest for this review is as follows:

- Iptacopan (Novartis)
- Danicopan (AstraZeneca: Alexion Pharmaceuticals) added to C5 inhibitor therapy

Comparators

Data permitting, we intend to compare all the agents to each other and to the following:

- C5 inhibitors:
    - Ravulizumab (Ultomiris®, Alexion Pharmaceuticals)
    - Eculizumab (Soliris®, Alexion Pharmaceuticals)
- Pegcetacoplan (Empaveli®, Apellis Pharmaceuticals)

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Hemoglobin improvement
    - Hemoglobin stabilization
    - Hemoglobin level
    - Transfusion avoidance or dependence
    - Thrombotic events
    - Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score
    - Health related quality of life
    - Lactate Dehydrogenase (LDH) level
    - Reticulocyte count
    - Major adverse cardiovascular events (MAVEs)
    - Death
    - Adverse events including
        - Breakthrough hemolysis
        - Neisseria infection
        - Treatment-related adverse events
- Other Outcomes
    - Laboratory measures including red blood cell, bilirubin, and haptoglobin profiles
    - Adverse events including
        - Abdominal pain
        - Iron deficiency

- Respiratory tract infection
- Viral infection

Timing

Evidence on intervention effectiveness will be derived from studies of any duration.

Settings

All relevant settings will be considered, including inpatient and outpatient settings in the United States.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.1. Categories of Contextual Considerations and Potential Other Benefits or Disadvantages

Contextual Consideration*
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability
Magnitude of the lifetime impact on individual patients of the condition being treated
Other (as relevant)

*Contextual considerations refer to social or ethical priorities that shape to some extent how the value of any effective treatments for a particular condition will be judged.

Potential Other Benefit or Disadvantage*
Patients' ability to achieve major life goals related to education, work, or family life
Caregivers' quality of life and/or 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
Society's goal of reducing health inequities
Other (as relevant)

*Potential other benefits or disadvantages are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

A detailed economic model analysis plan with proposed methodology, detailed model structure, model parameters, model inputs, and model assumptions will be published on October 18, 2023. This scoping document provides early thoughts about the overall model structure.

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of the treatments of interest relative to relevant comparator treatments. The model structure will be based in part on a literature review of prior published models of PNH. The base case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity impacts and other indirect costs will be considered in a separate analysis. This modified societal perspective analysis will be considered as a co-base case when the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per QALY, and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained. The target population will consist of patients with PNH who are eligible for Iptacopan or Danicopan and will include separate analyses for patients who are treatment-naïve and treated patients with clinically significant extravascular hemolysis. The model will likely consist of health states defined by hemoglobin levels, blood transfusion dependance, breakthrough hemolysis, spontaneous remission, and death. A cohort of patients will transition between states during predetermined cycles one month over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost-effectiveness will be estimated for shorter time horizons (e.g., five years).

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using relative effects of drug treatments on hemoglobin levels, blood transfusions, and breakthrough hemolysis from clinical trials.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of blood transfusions avoided, breakthrough hemolysis events avoided, life-years gained, quality-adjusted life years (QALYs) gained, and equal value of life years gained (evLYG). Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, productivity changes and other indirect costs will be included in a separate analysis if available data allow. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLYG, cost per life-year gained, and cost per breakthrough hemolysis events avoided. Given the

substantial potential for cost-offsets from standard of care, we will consider shared savings scenario analyses within this scope, in accordance with ICER's methods (see page 11, section 5).

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by Iptacopan or Danicopan (e.g., bone marrow transplants), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of PNH beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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