Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2676

iptacopan hard capsules (Fabhalta®)

Novartis Pharmaceuticals UK Limited

06 December 2024

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutics Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

iptacopan (Fabhalta®) is accepted for restricted use within NHSScotland.

Indication under review: As monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia.

SMC restriction: under the advice of the national PNH service.

In an open-label phase III study in patients with PNH who had persistent anaemia despite treatment with anti-C5 treatment iptacopan significantly increased the proportion of patients whose haemoglobin levels improved by at least 2 g/dL and the proportion of patients with haemoglobin levels greater than or equal to 12 g/dL, compared with anti-C5 treatment. In a single-arm phase III study in patients who had not received anti-C5 treatment, 92% of patients had an increase in haemoglobin of at least 2 g/dL after 24 weeks.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Iptacopan is a proximal complement inhibitor that targets Factor B (FB) to selectively inhibit the alternative pathway. Inhibition of FB in the alternative pathway of the complement cascade prevents C3 convertase activation, which prevents formation of C5 convertase. This helps to control both C3-mediated extravascular haemolysis (EVH) and terminal complement-mediated intravascular haemolysis (IVH). The recommended dose of iptacopan is 200 mg orally twice daily. See Summary of Product Characteristics.[1]

1.2. Disease background

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare, life-threatening condition that can affect people of any age, though it is most commonly diagnosed in young adults, typically in their 30s and 40s. The condition occurs due to an acquired mutation in the phosphatidylinositol glycan A (PIG-A) gene, leading to a deficiency of crucial terminal complement inhibitor proteins on cell surfaces. The absence of these proteins in blood cells triggers uncontrolled alternative complement activation, which can lead to the premature destruction of blood cells (haemolysis), haemolytic anaemia, thrombosis, and ultimately, death. Haemolysis in PNH occurs in two forms: within the blood vessels (IVH) or outside the blood vessels (EVH). IVH can lead to thrombosis which, before the availability of complement inhibitors, was the leading cause of death in patients with PNH.[2, 3]

1.3. Treatment pathway and relevant comparators

There is a national PNH service based in England that has agreements in place to provide support to patients with PNH in Scotland, and there is a PNH outreach centre based in NHS Lanarkshire. The management of patient with PNH in Scotland is guided by the national PNH service in England and shared care agreements with local haematology units.[3] The current standard of care for newly diagnosed PNH are the C5 inhibitors, ravulizumab (SMC2305) or eculizumab. Ravulizumab is given every 8 weeks and is more commonly prescribed than eculizumab which is given every 2 weeks; eculizumab is the preferred treatment during pregnancy. The inhibition of C5 helps to control intravascular haemolysis; extravascular haemolysis is believed to be mediated by C3 fragment deposition in PNH red blood cells. Approximately 20% of patients who are treated with C5 inhibitors experience clinically significant extracellular haemolysis.[2] The C3 inhibitor pegcetacoplan (SMC2451) was accepted for restricted use by SMC for the treatment of adult patients with PNH who are anaemic after treatment with a C5 inhibitor for at least 3 months (under the advice of the National PNH Service).

1.4. Category for decision-making process

Eligibility for interim acceptance decision option

Iptacopan received an Innovation Passport allowing entry into the Innovative Licensing and Access Pathway (ILAP) from the Medicines and Healthcare Products Regulatory Agency.

Eligibility for a PACE meeting

Iptacopan meets SMC orphan criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of iptacopan for the treatment of adult patients with PNH who have haemolytic anaemia comes from APPLY-PNH and APPOINT-PNH. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies[4, 5]

Criteria	APPLY-PNH	APPOINT-PNH
Study design	Randomised, open-label, phase III study	Single-arm phase III study
Eligible patients	• 18 years or older • PNH (confirmed by affected red-cell and white-cell populations of at least 10% of the total corresponding counts, detected by flow cytometry) • Hb levels <10 g/dL • No evidence of bone marrow failure • APPLY-PNH: Patients had received eculizumab or ravulizumab in a stable regimen for at least 6 months before randomisation • APPOINT-PNH: Patients who had not received complement inhibitor therapy and had LDH levels >1.5 times the upper limit of normal	
Treatments	Iptacopan 200 mg orally twice daily monotherapy or continue intravenous anti-C5 therapy (eculizumab or ravulizumab). The randomised treatment period was 24 weeks.	Iptacopan 200 mg orally twice daily monotherapy.
Randomisation	Randomised in an 8:5 ratio, stratified according to anti-C5 therapy and whether a red-cell transfusion had been received in the preceding 6 months (yes or no).	Not applicable.
Primary outcome	• Increase from baseline Hb levels ≥ 2 g/dL (assessed between Day 126 and Day 168) in the absence of RBC transfusion between Day 14 and Day 168. • Hb levels ≥ 12 g/dL (assessed between Day 126 and Day 168) in the absence of RBC transfusion between Day 14 and Day 168 (secondary outcome in APPOINT-PNH).	
Secondary outcomes	Transfusion avoidance between day 14 and day 168; average change in Hb from baseline; improvement in fatigue from baseline using FACIT-Fatigue questionnaire; average change in ARC from baseline; rate of clinical BTH; rates of MAVEs including thrombosis; average percent change in LDH levels from baseline.	
Statistical analysis	Multiplicity was adjusted for with the use of a weighted permutation test (primary outcomes) and a sequentially rejective testing procedure (secondary outcomes).	The lower boundary of the 95% CI of the primary outcome was compared with a prespecified threshold of 15%, which was derived from indirectly estimating Hb responses in two studies of C5 inhibitors.

Abbreviations: ARC = absolute reticulocyte count; BTH = breakthrough haemolysis; C5 = complement 5; CI = confidence interval; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; Hb = haemoglobin; LDH = lactate dehydrogenase; MAVE = major adverse vascular events; PNH = paroxysmal nocturnal haemoglobinuria; RBC = red blood cell.

In patients with PNH who had persistent anaemia despite treatment with anti-C5 treatment iptacopan significantly increased the proportion of patients whose haemoglobin levels improved by at least 2 g/dL and the proportion of patients with haemoglobin levels greater than or equal to 12 g/dL. In patients who had not received anti-C5 treatment, 92% of patients had an increase in haemoglobin of at least 2 g/dL at week 24 from baseline. See Table 2.2 for details.

Table 2.2. Selected primary and secondary outcomes of APPLY-PNH and APPOINT-PNH at Week 24 (Full Analysis Set).[4, 5]

	APPLY-PNH		**APPOINT-PNH**
	Iptacopan (n=62)[a]	**Anti-C5 treatment (n=35)**	**Iptacopan (n=40)[b]**
Co-primary outcome: Increase from baseline Hb levels ≥ 2 g/dL in the absence of RBC transfusion			
Proportion of responders (estimated)	82%*	2.0%	92%
Co-primary outcome: Hb levels ≥ 12 g/dL in the absence of RBC transfusion (secondary outcome in APPOINT-PNH)			
Proportion of responders (estimated)	69%*	1.8%	63%
Secondary outcome: Mean change in Hb from baseline			
Adjusted LSM change from baseline	3.6 g/dL*	-0.06 g/dL	4.3 g/dL
Secondary outcome: Transfusion avoidance			
Avoidance criteria met (estimated)	95%*	26%	98%
Secondary outcome: Mean change from baseline in FACIT-Fatigue score			
Adjusted LSM change from baseline	8.6*	0.3	10.8
Secondary outcome: Mean percentage change from baseline in LDH level			
Adjusted mean change from baseline	-3.5%	-2.4%	-84%
Secondary outcome: Mean change from baseline in ARC			
Adjusted LSM change from baseline ($x10^9$/L)	-115.8*	0.3	-82.5

[a] The co-primary outcomes were assessed in n=60 patients. In 2 patients with partially missing central haemoglobin data between days 126 and 168, the haematological response could not be established unequivocally and were therefore not included in these analyses.

[b] The haemoglobin response outcomes were assessed in n=33 patients due to missing data.

***** p<0.001 versus anti-C5 treatment group.

Abbreviations: ARC = absolute reticulocyte count; C5 = complement 5; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; Hb = haemoglobin; LDH = lactate dehydrogenase; LSM = least squares mean PNH = paroxysmal nocturnal haemoglobinuria; RBC = red blood cell.

In APPLY-PNH, 95/96 patients who completed the 24-week period entered the 24-week extension period. In patients who were randomised to iptacopan, mean haemoglobin levels achieved at week 24 (12.61 g/dL) were maintained at week 48 (12.19 g/dL). In patients who switched from anti-C5 treatment to iptacopan, mean haemoglobin increased from 9.15 g/dL at week 24 to 12.12 g/dL at week 48. In APPOINT-PNH, mean haemoglobin levels achieved at week 24 were also maintained up to week 48.[4]

2.2. Health-related quality of life outcomes

Health-related quality of life was assessed using three instruments in APPLY-PNH: FACIT-Fatigue (secondary outcome, see Table 2.2), EQ-5D-5L, and European Organisation for Research and Treatment of Cancer (EORTC)-QLQ-C30. A clear treatment benefit was observed with iptacopan versus anti-C5 treatment in functioning (physical and role) and symptom (fatigue and dyspnoea) subscales of EORTC-QLQ-C30 from baseline to day 168 and were congruent with the FACIT-Fatigue and EQ-5D-5L results.[4]

2.3. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing iptacopan with some of the relevant comparators, the submitting company presented an indirect treatment comparison. This was not used to inform the economic case. See Table 2.3 for details.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	**Complement inhibitor naïve:** Population adjusted ITC **Complement inhibitor experienced:** Population adjusted ITC
Population	**Complement inhibitor naïve:** ≥18y with PNH diagnosis who were naïve to complement inhibitors **Complement inhibitor experienced:** ≥18y with PNH diagnosis who were C5 inhibitor experienced with persistent anaemia
Comparators	**Complement inhibitor naïve:** Ravulizumab and eculizumab **Complement inhibitor experienced:** pegcetacoplan
Studies included	**Complement inhibitor naïve:** IPD from APPOINT-PNH and study level data from Study 301[6] **Complement inhibitor experienced:** IPD from APPLY-PNH and study level data from PEGASUS[7]
Outcomes	**Complement inhibitor naïve:** Transfusion avoidance, percent change from baseline in LDH and change from baseline in FACIT-fatigue score **Complement inhibitor experienced:** Percent change from baseline in haemoglobin, Transfusion avoidance, change from baseline in LDH and change from baseline in FACIT-fatigue score
Results	**Complement inhibitor naïve:**

	Patients in the iptacopan group had a greater reduction from baseline in the LDH compared with both ravulizumab and eculizumab (% change from baseline in LDH: iptacopan versus ravulizumab = -8.24 [95% CI: -13.28 to -3.20]; iptacopan versus eculizumab -9.06 [95% CI: -14.14 to -3.98]). Differences in transfusion avoidance (iptacopan versus ravulizumab OR = 1.32 [95% CI: 0.47 to 3.73]; iptacopan versus eculizumab OR = 1.88 [95% CI: 0.67 to 5.28]) and change from baseline in FACIT-fatigue score (iptacopan versus ravulizumab mean difference = 3.78 [95% CI: -1.38 to 8.94]; iptacopan versus eculizumab mean difference = 4.45 [95% CI: -0.72 to 9.62]) had confidence intervals that crossed 0/1 suggesting no evidence of a difference. **Complement inhibitor experienced:** In the unanchored analyses, iptacopan was superior to pegcetacoplan for change from baseline in Hb (mean difference [excluding post-transfusion data] = 1.01 [95% CI: 0.21 to 1.82]), and transfusion avoidance (OR = 12.71 [95% CI: 1.87 to 86.22]).[8] For change from baseline in LDH and FACIT-Fatigue confidence intervals crossed 0 suggesting no evidence of a difference. Anchored analyses are not reflected in this document due to validity concerns.

Abbreviations: ITC = indirect treatment comparison, IPD = individual patient data, PNH = paroxysmal nocturnal haemoglobinuria; LDH = lactate dehydrogenase; Hb = haemoglobin, FACIT = functional assessment of chronic illness therapy – fatigue.

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

In the APPLY-PNH study (randomised treatment period), the median duration of treatment in both the iptacopan group and anti-C5 group was 5.6 months. Any treatment-emergent adverse event (AE) was reported by 82% (51/62) of patients in the iptacopan group and 80% (28/35) in the anti-C5 group; 9.7% and 14% respectively had a serious AE; there were no incidences in either treatment group of an AE leading to treatment discontinuation, interruption, or death. In the core 24-week treatment period of APPOINT-PNH, 10% of patients receiving iptacopan had a serious AE.[4]

The most frequently reported treatment-emergent AEs of any grade with an incidence >5% in the iptacopan group versus the anti-C5 group in the randomised treatment period of APPLY-PNH were: headache (16% versus 2.9%); diarrhoea (14% versus 5.7%); nasopharyngitis (11% versus 5.7%); nausea (9.7% versus 2.9%); COVID-19 (8.1% versus 26%); arthralgia (8.1% versus 2.9%); urinary tract infection (8.1% versus 2.9%); abdominal pain (6.5% versus 2.9%); blood lactate dehydrogenase increased (6.5% versus 8.6%); dizziness (6.5% versus 0%).[4]

Overall, regulatory authorities concluded that the safety profile of iptacopan is similar to anti-C5 treatments, with most AEs being mild in severity. There are outstanding uncertainties with the safety profile of iptacopan given the data available, such as the risk of serious infections. There

was an increase in headaches and dizziness with iptacopan compared with anti-C5 treatment, however while inconvenient these AEs do not pose a major hazard for patients.[4]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- APPLY-PNH was a randomised, open-label, phase III study in a rare condition, providing evidence for the use of iptacopan in patients with PNH who had persistent anaemia despite treatment with anti-C5 treatment. Iptacopan was associated with statistically significant and clinically meaningful improvements in haemoglobin levels at week 24 versus the ongoing use of anti-C5 treatment. Secondary outcomes including transfusion avoidance, changes in ARC, and changes in patient-reported fatigue scores were also supportive.[4, 5]
- Similar results were reported in APPOINT-PNH, a single-arm phase III study that investigated iptacopan in treatment-naïve patients with PNH.[5]
- Iptacopan is an oral treatment administered twice daily, which is a convenient route of administration. Currently available treatments are administered parenterally.[4, 5]

4.2. Key uncertainties

- There is a lack of direct evidence comparing iptacopan with some relevant comparators in Scottish clinical practice. In patients who are treatment-naïve, the most relevant comparators are the C5 inhibitors, ravulizumab and eculizumab. In patients who are already being treated with C5 inhibitors, the most relevant comparator is pegcetacoplan. In the comparative study, APPLY-PNH, patients were already receiving C5 inhibitors and either continued that treatment or switched to iptacopan on entry to the study. ITCs were presented by the submitting company to provide data to address this uncertainty:
    - The ITC for the complement inhibitor naïve population was an unanchored matching-adjusted indirect comparison (MAIC) which are inherently at risk of bias and confounding. The company was unable to match on haemoglobin in the complement inhibitor naïve population due to the analysis failing to converge, and furthermore haemoglobin-related efficacy outcomes were not assessed, making interpretation of relative efficacy difficult.
    - For the complement inhibitor experienced population, the submitting company presented both anchored and unanchored analyses. The anchored analyses were limited by the differences in the common control groups, since patients in the PEGASUS study received a combination of treatments in the 4-week run-in period and patients in APPLY-PNH received C5 inhibitor monotherapy. There were notable differences in the study populations even after adjustment, and the effective sample size was considerably reduced (from n=62 to n=15 in APPLY-PNH) suggesting poor overlap between study populations. Given these limitations, the results should be interpreted with caution.

- There is limited long-term efficacy and safety data for iptacopan. Evidence beyond 24 weeks is limited by the lack of a control group and there is no data available beyond week 48. This is particularly relevant in a chronic condition such as PNH. Further data are awaited.[4]
- The study populations had a limited sample size (n=97 and n=40 in APPLY-PNH and APPOINT-PNH respectively), which may be expected given the rarity of PNH.[5]
- APPLY-PNH and APPOINT-PNH were open-label studies. This potential bias was limited by the objective measurement of haemoglobin and prespecified transfusion criteria, however patient-reported outcomes should be interpreted with caution.[5]

4.3. Innovative Licensing and Access Pathway (ILAP) and ongoing studies

Ongoing studies of iptacopan include: NCT04747613, a single-arm, open-label, multicentre, roll-over extension study to characterise long-term safety and efficacy of iptacopan in PNH, and to provide access to iptacopan to patients who have completed phase II/III studies (estimated completion date October 2027)[9]; APPULSE (NCT05630001), a single-arm, open-label, multicentre study evaluating the efficacy and safety of iptacopan in adult patients with PNH who have a mean Hb level ≥10 g/dL while being treated with a C5 inhibitor and then switch to iptacopan (estimated completion date January 2025).[10]

4.4 Service implications

There are no major service implications anticipated with the introduction of iptacopan. Iptacopan is taken orally which may be preferrable for patients and have benefits for the service over the comparators which are given as intravenous or subcutaneous infusions.

5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from PNH Scotland, which is a registered charity.
- PNH Scotland has not received any pharmaceutical company funding in the past two years.
- PNH is a debilitating, incurable condition that leaves patients exhausted, in pain and at risk of death due to thrombosis. Patients experience debilitating symptoms of fatigue, difficulty swallowing, erectile dysfunction, muscle weakness and abdominal pain, all of which can limit their daily functioning, with impacts on relationships, families and employment.
- Currently patients on complement inhibitor treatment receive the monoclonal antibody medicines eculizumab or ravulizumab. Both treatments are C5 complement inhibitors administered as an intravenous infusion. Patients who experience haemolysis while on a C5 complement inhibitor require pegcetacoplan which is a C3 complement inhibitor and is administered by subcutaneous infusion.

- Iptacopan is a self-administered medicine taken as a monotherapy. It is taken twice daily in tablet form. Moving to a tablet form of treatment would be extremely beneficial to most patients.

- Patients on iptacopan described experiencing greater energy levels and a better quality of life. Moving away from medicines requiring refrigeration and needles frees patients up to live a more normal life.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime horizon was used, which equated to 58 years for the complement inhibitor naïve population and 49 years for the complement inhibitor experienced population.
Population	Results for two patient populations were presented in line with the clinical evidence: • Adults with PNH who are complement inhibitor naïve and have haemolytic anaemia • Adults with PNH who are complement inhibitor experienced and have persistent haemolytic anaemia
Comparators	For the complement inhibitor naïve population, ravulizumab was the key comparator. For the complement inhibitor experienced population, the comparators were ravulizumab and pegcetacoplan. A comparison with eculizumab was also provided for both populations for completeness.
Model description	A semi-Markov model was used which comprised four mutually exclusive health states: • No transfusion and no anaemia • No transfusion and anaemia • Transfusion • Death Subsequent treatment was also modelled for patients who discontinued initial treatment. The Hb threshold used in the model was <10.5g/dL.
Clinical data	For the complement inhibitor naïve population, the main clinical data source was APPOINT-PNH. Individual patient data (IPD) from this study were used to estimate transition probabilities for iptacopan patients capturing both anaemia status and blood transfusion requirements with 48-week data used in the base case and 24-week data applied in sensitivity analysis. For the comparator C5 inhibitors, IPD were identified from a real-world retrospective cohort study in the UK and France (APPEX study) to derive transition probabilities for ravulizumab and eculizumab based on haematological response over a 6- month period. For the complement inhibitor experienced population, the main clinical data source was IPD from APPLY-PNH which were used to derive transition probabilities for iptacopan and C5 inhibitors. The base case used 48-week study data for iptacopan and 24-week data for the C5 inhibitors, with 24-week data for iptacopan explored in sensitivity analysis. For pegcetacoplan arm, transition probabilities were sourced from 16-week data from the PEGASUS study with adjustments made to the regression model used to derive the transition probabilities to align the APPLY-PNH data to the PEGUSUS trial population.

<table>
<tr><td>Extrapolation</td><td>Efficacy of the treatments included in the model was based on data up to 48 weeks (24 weeks for C5 inhibitors) with the treatment effect assumed to be maintained beyond this time point for the duration of the model.

Discontinuation was included for iptacopan and pegcetacoplan in the base case informed by treatment-specific all-cause discontinuation rates from the relevant studies. All patients were assumed to switch to ravulizumab. For iptacopan the discontinuation rate applied was 2.72% per year sourced from the 48-week analysis of APPLY-PNH. For pegcetacoplan, the rate applied was 16.13% based on PEGASUS. For eculizumab and ravulizumab, a one-time discontinuation rate was applied to the treatment naïve analysis to reflect clinical practice where experts noted around 30% of patients who continue to have anaemia after 6 months would switch to pegcetacoplan.</td></tr>
<tr><td>Quality of life</td><td>EQ-5D-5L data were collected in APPOINT-PNH and APPLY-PNH and were used to derive the utility values used in the model. These are summarised in the table below. Utility values for pegcetacoplan were assumed equal to iptacopan. A utility decrement of 0.11 was applied to capture the impact of breakthrough haemolysis (BTH) on patient quality of life.

Health state utility values used in model

<table>
<tr><td rowspan="2">Health State</td><td colspan="2">Iptacopan/pegcetacoplan</td><td colspan="2">C5 inhibitors</td></tr>
<tr><td>Mean</td><td>SE</td><td>Mean</td><td>SE</td></tr>
<tr><td>No Transfusion and No Anaemia</td><td>0.879</td><td>0.004</td><td>0.775</td><td>0.056</td></tr>
<tr><td>No Transfusion and Anaemia</td><td>0.822</td><td>0.008</td><td>0.743</td><td>0.015</td></tr>
<tr><td>Transfusion</td><td>0.791</td><td>0.015</td><td>0.695</td><td>0.021</td></tr>
</table>
Note: Anaemia defined as Hb <10.5 g/dL. Abbreviation: SE, standard error.</td></tr>
<tr><td>Costs and resource use</td><td>Medicine costs included acquisition, administration and subsequent treatment costs were included. Costs were also included for vaccinations, antibiotics and iron overload treatments associated with complement inhibitor treatments. No adverse event costs were applied in any treatment arm. Health state resource use included blood transfusions, haematologist visits and blood tests.</td></tr>
<tr><td>PAS</td><td>A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. PAS discounts are in place for ravulizumab and pegcetacoplan and these were included in the results used for decision-making by using estimates of the comparator PAS price.</td></tr>
</table>

6.2. Results

SMC considered results for decision-making that took into account all relevant PAS. SMC is unable to present these results due to competition law issues.

The QALY gains for iptacopan estimated from the cost-effectiveness model were 1.14 versus ravulizumab and 1.15 versus eculizumab in the complement inhibitor naïve patients. In the complement inhibitor experienced patients the QALY gains were 1.82 versus both ravulizimab and eculizumab and 1.13 versus pegcetacoplan.

6.3. Sensitivity analyses

A range of sensitivity and scenario analyses were considered, and descriptions of these key scenarios are provided in tables 6.2 and 6.3 below.

Table 6.2 Sensitivity and Scenario Analysis Results - complement inhibitor naïve patients

	Parameter	Base case	Scenario
	Base case		
1	Definition of anaemia	<10.5g/dL	<10g/dL
2	Missing data from APPEX	Imputation using LOCF	No imputation
3	Discontinuation rates	Study rates and clinical opinion	No discontinuation for any treatment
4			No discontinuation for iptacopan
5			Pooled discontinuation rate for iptacopan
6	Utility values	Treatment dependent utilities (higher utility values used for iptacopan and pegcetacoplan)	Health state dependent utilities applied to all treatments
7	Study data	48-week	24-week
8	Time horizon	Lifetime	30 years
9			20 years

Abbreviations: BSC = best supportive care; Incr. = Incremental; ICER =incremental cost-effectiveness ratio; LOCF = last observation carried forward; PFS = progression free survival; QALY = quality-adjusted life year; RDI =Relative dose intensity

Table 6.3 Sensitivity and Scenario Analysis Results -complement inhibitor experienced patients

	Parameter	Base case	Scenario
	Base case		
1	Definition of anaemia	<10.5g/dL	<10g/dL
2	Discontinuation rates	Study rates and clinical opinion	No discontinuation for any treatment
3			10% rate for pegcetacoplan
4	Utility values	Treatment dependent utilities	Health state dependent utilities
5	Study data	48-week	24-week
6	C5 inhibitor efficacy	Assumed equivalent	Applied by treatment
7	Time horizon	Lifetime	30 years
8			20 years

Abbreviations: BSC = best supportive care; Incr. = Incremental; ICER =incremental cost-effectiveness ratio; LOCF = last observation carried forward; PFS = progression free survival; QALY = quality-adjusted life year; RDI =Relative dose intensity

6.4. Key strengths

- The comparators included for each patient population are appropriate and reflect Scottish practice.
- The availability of EQ-5D data collected in the APPOINT-PNH and APPLY-PNH studies is a key strength.

6.5. Key uncertainties

- There is a lack of comparative data to support improved efficacy with iptacopan versus C5 inhibitors in the naïve population and versus pegcetacoplan in the experienced population. ITCs were conducted but the outcomes were not used directly in the economic model. Instead, in the complement inhibitor naïve population transition probabilities were derived from IPD from the APPOINT-PNH study for the iptacopan arm, and from IPD from a real-world study (APPEX) for the C5 inhibitor arm. In the complement inhibitor experienced population IPD from APPLY-PNH were used to estimate transition probabilities for the iptacopan and C5 inhibitor arms, with published transition probabilities from the PEGUSUS study used for the pegcetacoplan arm. The ITCs are therefore considered supportive only meaning it is difficult to fully validate the incremental QALY gains estimated for iptacopan.
- The model assumes a continued treatment effect but there is a lack of long-term data to support this, and no treatment waning was explored through sensitivity analysis. This approach has been accepted previously in the pegcetacoplan and ravulizumab submissions, but remains a source of uncertainty. The company noted that any waning of the treatment effect would apply to all treatments in the model and highlighted that there was no reduction in efficacy observed between the 24- and 48-week analyses from the studies.
- The results in the complement inhibitor experienced population are particularly sensitive to the discontinuation assumptions applied in the model with a QALY loss (-0.07) estimated for iptacopan versus pegcetacoplan when no discontinuation is assumed (table 6.3, scenario 2). The company noted that this scenario would not reflect practice where patients would discontinue and receive subsequent treatments. Additional sensitivity analysis was also provided using a lower discontinuation rate for pegcetacoplan (table 6.3, scenario 3) where the conclusion remained unchanged compared to the base case.
- Treatment-specific utility values were used meaning patients in the iptacopan and pegcetacoplan arms of the model experienced improved quality of life compared to those on C5 inhibitors in the same health state. The company provided evidence to justify this approach and explored health state specific utility values in sensitivity analysis. In this scenario the QALY gain was reduced to 0.41 (from 1.14) vs ravulizumab in complement inhibitor naïve patients (table 6.2, scenario 6) and 0.74 (from 1.13) vs pegcetacoplan in complement inhibitor experienced patients (table 6.3 scenario 4), however the overall conclusion was unchanged from the base case.
- The cost of eculizumab in practice is lower than the published price used in the model as a national contract framework price is in place. It is noted the price used in the base case is

consistent with SMC process and also that eculizumab is not the key comparator for either patient population.

- The Hb threshold used in model does not match the inclusion criteria in the study but sensitivity analysis showed this was a minor issue given the small differences between the thresholds used (scenario 1 in tables 6.2 and 6.3).
- The model assumes ravulizumab and eculizumab have comparable efficacy, which is a source of uncertainty in the analysis. However, this approach has been accepted in previous submissions.

*Other data were also assessed but remain confidential.**

7. Conclusion

After considering all the available evidence, the Committee accepted iptacopan for restricted use in NHSScotland.

8. Guidelines and Protocols

The National PNH Service was established in April 2009 to care for and support patients with PNH from throughout England. There are agreements in place with the Healthcare Commissioners in Scotland, Wales and Northern Ireland for the National PNH Service to provide support to patients with PNH from the rest of the UK. The PNH Service is now funded by NHS England as a Highly Specialised Service. The management of PNH in Scotland is largely guided by the National PNH Service in England and shared care agreements with local haematology units.[3]

9. Additional Information

9.1. Product availability date

04 September 2024

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
iptacopan	**200 mg orally twice daily**	**£344,500**

Costs from BNF online on 22 November 2024. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish the budget impact due to commercial-in-confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen

*Other data were also assessed but remain confidential.**

References

1. Novartis Pharmaceuticals UK Ltd. Iptacopan (Fabhalta) hard capsules. Summary of product characteristics (SPC). Electronic Medicines Compendium. www.medicines.org.uk Last updated 16 August 2024. .
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This assessment is based on data submitted by the applicant company up to and including 14 November 2024.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial-in-confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards

are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.