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SMC2451

pegcetacoplan 1,080mg solution for infusion (Aspaveli®)

Swedish Orphan Biovitrum Ltd

10 June 2022

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

pegcetacoplan (Aspaveli®) is accepted for restricted use within NHSScotland.

Indication under review: in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who are anaemic after treatment with a C5 inhibitor for at least 3 months.

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

In an open-label, randomised, phase III study in patients anaemic after at least 3 months treatment with a C5 inhibitor, there was a significantly greater improvement in haemoglobin levels after 16 weeks of treatment with pegcetacoplan compared with continued C5 inhibitor treatment.

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

Chairman
Scottish Medicines Consortium

Indication

In the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who are anaemic after treatment with a C5 inhibitor for at least 3 months.[1]

Dosing Information

Pegcetacoplan is administered twice weekly as a 1,080mg subcutaneous infusion with a commercially available syringe infusion pump that can deliver doses up to 20mL. The twice weekly dose should be administered on day 1 and day 4 of each treatment week. The dosing regimen may be changed to 1,080mg every third day (day 1, 4, 7, 10, 13 and so forth) if a patient has a lactate dehydrogenase (LDH) level greater than two times the upper limit of normal. In the event of a dose increase, LDH should be monitored twice weekly for at least 4 weeks.

For patients switching to pegcetacoplan from a C5 inhibitor, for the first 4 weeks, pegcetacoplan is administered as twice weekly subcutaneous doses of 1,080mg in addition to the patient's current dose of C5 inhibitor treatment to minimise the risk of haemolysis with abrupt treatment discontinuation. After 4 weeks, the patient should discontinue the C5 inhibitor before continuing on monotherapy with pegcetacoplan.

PNH is a chronic disease and treatment with pegcetacoplan is recommended to continue for the patient's lifetime, unless discontinuation is clinically indicated.

Pegcetacoplan should be initiated under the supervision of a healthcare professional experienced in the management of patients with haematological disorders.

Pegcetacoplan can be given by a healthcare professional or administered by the patient or caregiver following proper instruction. Self-administration and home infusion should be considered for patients who have tolerated treatment well in experienced treatment centres. The decision of a possibility of self-administration and home infusions should be made after evaluation and recommendation from the treating physician.[1]

Product availability date

08 April 2022

Pegcetacoplan meets SMC orphan criteria.

Summary of evidence on comparative efficacy

Paroxysmal nocturnal haemoglobinuria (PNH) is a very rare and life-threatening condition that results in uncontrolled complement activation and systemic complications, which include chronic haemolysis, impaired bone marrow function and thrombosis. Pegcetacoplan is a pegylated cyclic peptide inhibitor of complement C3 which acts to exert a broad inhibition of the complement cascade thereby controlling the mechanisms leading to extravascular and intravascular haemolysis.[1,2]

The evidence comes from one randomised, open-label, phase III study (PEGASUS) comparing the efficacy and safety of pegcetacoplan with eculizumab. Eligible patients were aged ≥18 years with a diagnosis of PNH confirmed by high-sensitivity flow cytometry. They had been receiving a stable dose of eculizumab for ≥3 months and had a haemoglobin level <10.5g/dL. All patients entered a 4-week run-in period when they received pegcetacoplan (1,080mg by subcutaneous infusion twice weekly) in addition to their current stable dose of eculizumab. After 4 weeks, patients were randomised equally to receive either pegcetacoplan (1,080mg twice weekly, increased to 1,080mg every 3 days if needed) or their current dose of eculizumab for a 16-week controlled treatment period. Randomisation was stratified according to the number of packed red blood cell (PRBC) transfusions in the year before the run-in (<4 or ≥4) and platelet count at screening (<100,000/mm^3 or ≥100,000/mm^3).[2,3]

The primary outcome was the change in haemoglobin level from baseline to week 16 assessed in the intention to treat (ITT) population, censored for patients who required a transfusion. A hierarchical statistical strategy tested the primary outcome for superiority, the key secondary outcomes for non-inferiority and, if met for all outcomes, then for superiority. The key secondary outcomes (measured from baseline to week 16) were proportion of patients not requiring a transfusion (transfusion avoidance); the change in absolute reticulocyte count (ARC); the change in lactate dehydrogenase (LDH) level and the change in the Functional Assessment of Chronic illness Therapy (FACIT)-Fatigue score. The primary outcome, change in haemoglobin level, was significantly higher in the pegcetacoplan group compared with the eculizumab group.

Pegcetacoplan was found to be non-inferior to eculizumab for transfusion avoidance and change in ARC but not for change in LDH. Therefore, the non-inferiority for FACIT-Fatigue score was not tested nor was superiority for any of the key secondary outcomes. Other secondary outcomes, assessed between baseline and week 16, also numerically favoured pegcetacoplan over eculizumab. These included haemoglobin response (defined as an increase of ≥1g/dL in haemoglobin in absence of transfusions), reticulocyte normalisation (defined as an ARC reticulocyte count above the ULN), haemoglobin normalisation (defined as a haemoglobin level above the ULN), change in indirect bilirubin and haptoglobin levels and number of units of packed red blood cells (PRBC) transfused.[2,3] Details are presented in table 1.

Table 1: Results for the primary and secondary outcomes of PEGASUS study in ITT population[2,3]

	Pegcetacoplan (n=41)	**Eculizumab (n=39)**	**Mean difference (95% CI), p-value**
Primary outcome			
Change in haemoglobin from baseline to week 16, adjusted least squares mean, g/dL	2.37	-1.47	3.84 (2.33 to 5.34), p<0.001

Key secondary outcomes			
Transfusion avoidance to week 16, % (n/N)	85% (35/41)	15% (6/39)*	63% (48% to 77%)[A]
Change in absolute reticulocyte count from baseline to week 16, cells/L	-135.82 x 10^9	27.29 x 10^9	-163.61 x 10^9 (-189.91 to -137.30 x 10^9)[A]
Change in LDH from baseline to week 16, units/L	-14.76	-10.12	-4.63 (-181.30 to 172.04)[B]
Change in FACIT-F score from baseline to week 16	9.22	-2.65	11.87 (5.49 to 18.25)
Other secondary outcomes			
Haemoglobin response	76%	0	-
Reticulocyte normalisation	78% (32/41)	2.6% (1/39)	-
Haemoglobin normalisation	34% (14/41)	0	-
Change in indirect bilirubin level, micromol/L	-17.78	4.15	-
Change in haptoglobin level, g/L	-0.02	0.12	-
Mean number of PRBC units transfused	0.6	5.1	-

* In total, three patients in the eculizumab group received transfusion despite not meeting the criteria with pre-transfusion haemoglobin levels being >9.0 g/dL; [A] non-inferiority demonstrated; [B] non-inferiority not demonstrated; CI=confidence interval; FACIT-F= Functional Assessment of Chronic Illness Therapy-Fatigue; ITT=intention to treat; LDH=lactate dehydrogenase; PRBC=packed red blood cells

As well as the FACIT-Fatigue score, quality of life was assessed using the additional secondary outcomes of Linear Analog Scale Assessment (LASA) scores (a three item questionnaire with which patients assess their level of functioning; score 0 to 300) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Scale (EORTC-QLQ-C30) global status score (range 0 to 100). The least square mean change from baseline to week 16 in LASA scores increased (improved) by 49.4 in the pegcetacoplan group and decreased (worsened) in the eculizumab group by -9.7. The least square mean change from baseline to week 16 in EORTC-QLQ-C30 global status score increased (improved) by 15.9 in the pegcetacoplan group and decreased (worsened) in the eculizumab group by -2.7.[2]

After the 16-week controlled period, patients could enter a 32-week open-label period when all patients received pegcetacoplan; those treated with eculizumab during the controlled period received eculizumab plus pegcetacoplan for the first 4 weeks (weeks 17 to 20). Seventy-seven patients entered the open-label period (38 from the pegcetacoplan group and 39 from the eculizumab group) and 67 patients completed to week 48 (35 and 32 patients respectively). Results to week 48 confirmed the improvements from the controlled period. At week 48, the mean observed change in haemoglobin from baseline was 2.7g/dL and 71% (55/77) of patients did not require a transfusion (82% of patients who continued on pegcetacoplan and 62% of patients who switched from eculizumab to pegcetacoplan). Improvements in FACIT-Fatigue score were confirmed through Week 48 with 55% of patients improved FACIT-Fatigue score by ≥3 points.[2,4]

The submitting company presented an anchored matching adjusted indirect comparison (MAIC) of pegcetacoplan with ravulizumab in adult patients with PNH who had previously been treated with eculizumab. This used individual patient level data from the PEGASUS study to adjust the study population to match the aggregate data from Study 302 (ravulizumab versus eculizumab).[3,10] The MAIC results are presented in the company submission and the published findings suggest that clinical, haematological and quality of life outcomes were better for patients treated with pegcetacoplan compared with ravulizumab.[5] However, there were key differences between the studies that could not be matched (including treatment period, eculizumab dose and run-in) and between the study populations (including haemoglobin level and number of PRBC transfusions at baseline). The company acknowledged these limitations and did not use the MAIC results in the economic analysis.

Summary of evidence on comparative safety

During the 4-week, run-in period of PEGASUS when all patients received pegcetacoplan plus eculizumab (n=80), a treatment-emergent adverse event (AE) was reported by 86% of patients and these were considered related to pegcetacoplan in 55%. A serious AE was reported in one patient and there were no discontinuations due to AEs. The most frequently reported treatment emergent AEs of any grade were: injection site reactions (58%, including injection site erythema, pruritus and swelling); gastro-intestinal disorders (20%) including diarrhoea (7.5%) and nausea (6.3%); nervous system disorders (18%) including headache (12%) and infections and infestations (14%).[2]

During the 16-week, randomised, controlled period, a treatment-emergent AE was reported in 88% (36/41) of patients in the pegcetacoplan group and 87% (34/39) of patients in the eculizumab group and these were considered related to pegcetacoplan in 39% of patients and related to eculizumab in 18% of patients. A serious AE was reported in 17% of pegcetacoplan patients and 15% of eculizumab patients and three patients (7.3%) in the pegcetacoplan group and no patients in the eculizumab group discontinued due to an AE. During the controlled period, the most frequently reported treatment-emergent AEs of any grade in the pegcetacoplan versus eculizumab groups respectively were: haemolysis (9.8% versus 23%), headache (7.3% versus 23%), diarrhoea (22% versus 2.6%), injection site erythema (17% versus 0%), fatigue (4.9% versus 15%), anaemia

(0% versus 13%), abdominal pain (12% versus 10%), injection site reaction (12% versus 0%), back pain (7.3% versus 10%), dizziness (2.4% versus 10%) and injection site welling (10% versus 0%).[2,3] During the 32-week, open-label period, when all patients received pegcetacoplan, a treatment-emergent AE was reported by 91% (70/77) of patients and these were considered related to pegcetacoplan in 43% of patients. A serious AE was reported in 23% of patients and nine patients (12%) discontinued due to an AE. The most frequently reported treatment emergent AEs of any grade during open-label treatment with pegcetacoplan were: haemolysis (19%), nasopharyngitis (16%), diarrhoea (14%), injection site erythema (12%), cough (10%), headache (10%), fatigue (10%) and upper respiratory tract infection (10%).[2]

Summary of clinical effectiveness issues

PNH is a very rare and life-threatening condition which can occur at any age but is most often diagnosed in young adults, generally in their 30s and 40s. It occurs due to an acquired mutation in the phosphatidylinositol glycan A (PIG-A) gene which results in a lack of key naturally occurring, terminal complement inhibitor proteins on cell surfaces. Their absence in blood cells results in uncontrolled alternative complement activation and systemic complications which include chronic haemolysis, impaired bone marrow function and thrombosis. Thromboembolic events are the leading cause of death in patients with PNH. The severity of PNH is variable and not all patients require active complement inhibitor therapy. Patients with less severe disease can be treated with supportive therapies including folic acid and iron tablets, while patients with more severe disease may require RBC transfusions and anticoagulants. Life-long treatment is generally required. The only curative treatment is allogeneic stem cell transplantation but this is rarely used as it is associated with a high level of morbidity and mortality. [2,6]

In Scotland, patients with PNH are managed by the PNH National Service in consultation with their local haematologist and are referred to the national service via an outreach clinic in Monklands Hospital.[6] Eculizumab was the first treatment with a marketing authorisation for the treatment of PNH.[7] However, it was not recommended for use by SMC (SMC 1130/16). Patients in Scotland have received eculizumab under patient Peer Approved Clinical System Tier 1 (PACS1) application and under the direction of the PNH National Service and in-line with these recommended indications for eculizumab treatment. Ravulizumab was licensed for the treatment of PNH in adult patients with haemolysis and clinical symptom(s) indicative of high disease activity and in adult patients who are clinically stable after having been treated with eculizumab for at least the past 6 months. It is structurally similar to eculizumab but requires less frequent administration.[8] SMC accepted ravulizumab for restricted use under the advice of the national PNH service (SMC2305). The C5 inhibitors, eculizumab and ravulizumab, only act to control intravascular haemolysis and do not control extravascular haemolysis. Therefore, despite treatment with eculizumab or ravulizumab some patients may remain symptomatic and need red blood cell transfusions.[2,6] Pegcetacoplan meets SMC orphan criteria.

Evidence from the phase III PEGASUS study demonstrated that pegectacoplan is superior to eculizumab in improving haemoglobin levels after 16 weeks. The primary analysis censored data for the use of transfusions and more patients in the eculizumab group (n=33) received transfusions during the controlled period than in the pegcetacoplan group (n=5); although three patients in the eculizumab group received a transfusion despite haemoglobin levels above the pre-specified threshold of 9.0 g/dL. The results were confirmed in additional sensitivity analyses imputing missing data and supportive analyses using all observed data; however the treatment effect was smaller but still statistically significant and clinically relevant.[2] Results for the primary outcome were supported by a higher proportion of pegcetacoplan-treated patients avoiding the need for transfusions, a clinically relevant outcome. In-line with the hierarchical testing strategy, only results for the primary outcome were tested for superiority of pegcetacoplan over eculizumab. Pegcetacoplan was non-inferior to eculizumab for transfusion avoidance and change in ARC but since the change in LDH did not meet the criteria for non-inferiority, the non-inferiority for FACIT-Fatigue score was not tested nor was superiority for any of the key secondary outcomes. Results numerically favoured pegcetacoplan over eculizumab.[2,3]

The PEGASUS study was small and of open-label design which is prone to bias but outcome measurements were made by blinded central laboratory staff. The co-administration of eculizumab plus pegcetacoplan during the initial 4-week run-in period before randomisation, may have introduced selection bias. However, since no patients discontinued study treatment during this period, this was not considered to have affected the results. The co-administration during the run-in period may have affected the relative treatment effect, which appeared smaller at week 2 of the randomised controlled period. The controlled treatment period was limited to 16 weeks and this is short for a chronic treatment. It may not fully capture the relative treatment effect on haematological parameters and on the need for transfusions and resulting treatment for iron overload. Uncontrolled data from the 32-week, open-label period suggests that the treatment effect is maintained to week 48. Further long-term safety data are needed to characterise the safety profile of pegcetacoplan. [2]

The baseline characteristics were generally balanced between the treatment groups. However, despite randomisation, some differences remained between the pegcetacoplan and eculizumab groups, including shorter median time since diagnosis (6.0 years versus 9.7 years), more patients receiving doses of eculizumab above 900mg every 2 weeks (35% versus 23% respectively), mean LDH levels being slightly lower (257.5 units/L versus 308.6 units/L respectively), mean haptoglobulin levels being higher (0.144 versus 0.125 g/L respectively) and fewer patients having received at least four transfusions (51% versus 59% respectively). These differences may suggest that the patients in eculizumab group had less well-controlled disease than those in the pegcetacoplan group. The results observed in the eculizumab group of PEGASUS were smaller than those from other eculizumab studies; however due to differences between studies it was not possible to conclude underperformance of eculizumab in PEGASUS.[2]

Patients enrolled in the PEGASUS study had a haemoglobin level <10.5g/dL despite receiving ≥3 months of stable doses of eculizumab. The licensed indication for pegcetacoplan is for patients with PNH who are anaemic after ≥3 months of treatment with a C5 inhibitor without a specified

haemoglobin level and patients considered anaemic with a higher haemoglobin level would be eligible for pegcetacoplan in clinical practice. The dose of eculizumab used by study patients was higher than the licensed dose in 30% of patients and the size of the treatment effect may not be generalisable to patients who had been using the licensed dose in practice. In addition, study patients had been on stable doses of eculizumab for ≥3 months and while the licensed indication would allow patients previously treated with ravulizumab to receive pegcetacoplan, there is no evidence to support this. Ravulizumab is structurally similar to eculizumab and has been found to be non-inferior to it.[1-3]

The PEGASUS study compared pegcetacoplan with eculizumab and there are no direct data comparing pegcetacoplan with ravulizumab. The company did perform an anchored MAIC to compare with ravulizumab but this was not used in the economic analysis. Instead, equal efficacy between ravulizumab and eculizumab was assumed and the results for eculizumab from the PEGASUS study were used for ravulizumab. Two phase III non-inferiority studies support this assumption but in different patient populations. The European Medicines Agency accepted this assumption noting that eculizumab and ravulizumab share the same mechanism of action.[2,9,10]

The introduction of pegcetacoplan would offer a treatment for patients who remain anaemic after treatment with a C5 inhibitor and may reduce the need for continued transfusions. Pegcetacoplan is administered by subcutaneous infusion. This allows the potential for patients or caregivers to self-administer pegcetacoplan, an option that is not possible for ravulizumab and eculizumab which are both administered by intravenous infusion by a healthcare professional. Pegcetacoplan is administered more frequently than eculizumab and ravulizumab.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis covering pegcetacoplan's full licenced indication. Pegcetacoplan was compared with the continued use of either one of two C5 inhibitors, eculizumab or ravulizumab. Given the licenced indication, these appeared to be the appropriate comparators.

Evidence for the comparison of pegcetacoplan and eculizumab came from the phase III randomised controlled study, PEGASUS.[2, 3] As noted above, the company attempted an indirect comparison to inform the relative efficacy versus ravulizumab, however, the analysis was associated with uncertainty. Given this, for the economic analysis, it was assumed that eculizumab and ravulizumab were equally effective at treating PNH. This assumption was supported by results from two studies,[9,10] clinical opinion received by the company and was the primary assumption in the economic evaluation of ravulizumab submitted to SMC[12].

The analysis employed a Markov model containing three health states and an absorbing death state. The health states were *no transfusion and haemoglobin (Hb) <10.5 g/dL*, *no transfusion and Hb ≥10.5 g/dL* and *transfusion required*. Additionally, the model included event states to capture intravascular breakthrough haemolysis (IVBTH), iron overload and AEs. All patients were assumed to start in the *no transfusion and Hb <10.5 g/dL* state at the start of the modelling period before

potentially moving on to other health states as the model progressed. Movements between the states were defined by transition probabilities, that were themselves created from analysis of the PEGASUS study data. These transition probabilities were held constant across the full 51 years of the model, assuming a consistent treatment effect.

Patient health related quality of life was measured during the PEGASUS study using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30). Despite being cancer focused, this instrument is frequently used in PNH. EORTC-QLQ-C30 values were converted into EQ-5D-3L values using a mapping algorithm from Longworth et al. (2014).[13] The disutility of AEs were assumed to be captured in the state-specific utility values, but additional disutilities for the intravenous administration of eculizumab and for iron chelation therapy were included. There was no assumed disutility of IVBTH.

The most significant element of costs was the procurement of the medicines themselves. No administration costs were included for those receiving eculizumab or ravulizumab, as these were assumed to be funded by the manufacturers of those medicines. Pegcetacoplan can be administered at home, so only costs of the first two administrations were included. The first dose was assumed to take place at hospital and the second dose at home, but under nurse supervision. Patients in the transfusion required state were modelled as receiving just under 2 units of blood each month, in line with the values recorded in the PEGASUS study. A major difference between those receiving pegcetacoplan or a C5 inhibitor was the treatment response to iron overload. Patients were assumed to suffer iron overload equally across the study arms, but the company assumed that those receiving pegcetacoplan had sufficient Hb levels to undergo venesection, although this practice was not matched in the central study. Those receiving eculizumab or ravulizumab were assumed to be treated with the much more expensive iron chelation therapies of deferasirox and desferrioxamine mesilate.

Wider resource use was limited, with patients assumed only to use haematologist consultations and blood tests. Additionally, there was a composite cost, averaging £393 for patients who discontinued pegcetacoplan because of IVBTH, resulting from some patients being hospitalised and some needing to undergo dialysis.

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. A PAS discount is in place for ravulizumab and this was included in the results used for decision-making by using estimates of the comparator PAS price.

The results presented do not take account of the PAS for ravulizumab or the PAS for pegcetacoplan but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for ravulizumab due to commercial confidentiality and competition law issues. As such, results are shown in the tables below at list prices.

Table 2: Comparative economic results (at list prices)

Comparison		Inc. LYs	ICER
From	To		
Eculizumab	Pegcetacoplan	0	£376,078
Ravulizumab	Pegcetacoplan	0	Dominant

Abbreviations: ICER – incremental cost-effectiveness ratio; LY – life years; QALYs – quality adjusted life years

In terms of the pattern of results, treatment with pegcetacoplan led to savings on transfusions, monitoring and the treatment of iron overload. Those receiving pegcetacoplan were modelled as being more likely to occupy the higher Hb state that is associated with higher utility and experience fewer disutilities, than those treated with a C5 inhibitor.

In addition to the base case results, the company has provided a selection of illustrative scenario analysis. These, are presented below at list prices:

Table 3: Scenario analysis results (list prices)

#	Parameter	Base case description	Scenario analysis description	ICER (£/QALY) pegcetacoplan vs eculizumab	ICER (£/QALY) pegcetacoplan vs ravulizumab
1	Time horizon	51 years	10 years	£362,515	Dominant
2			20 years	£364,287	Dominant
3	Utility decrement of eculizumab infusion	0.025	0.000	£450,938	Dominant
4			0.057	£310,170	Dominant
5	Utility decrement of iron chelation	-0.014	0.00	£385,945	Dominant
6	Data informing Transition probabilities	4-48-week study data for all cycles	0-4 weeks study date for first cycle; 4-48-week study data for subsequent cycles	£375,398	Dominant
7			4-16 week study data for all cycles	£368,612	Dominant
8	Number of pegcetacoplan administrations at clinic	1	2	£376,091	Dominant

Abbreviations: ICER – incremental cost-effectiveness ratio; LY – life years; QALYs – quality adjusted life years; RCP – Randomised control period (of PEGASUS study); Open label period (of PEGASUS study)

The strengths of the economic case were:

- Data on the comparison between pegcetacoplan and eculizumab were derived from a head-to-head randomised study.
- The company reports having validated extensive parts of the modeling approach and outcomes with clinical experts.

The main weaknesses of the economic case were:

- The PEGASUS clinical study was small with a short follow up period. This was particularly true of the randomised control period, where pegcetacoplan and eculizumab were compared head to head, which lasted only 16 weeks. This increased uncertainty on some of the modelling inputs.
- Within the model, ravulizumab was assumed to have equal efficacy to eculizumab. While there was evidence and clinical opinion to support this, it remained a source of uncertainty.
- The treatment effect was assumed constant across the duration of the model, without direct evidence to support long-term efficacy.
- The model structure may be too simplistic and ignore disease outcomes such as thrombosis and spontaneous remission. The company excluded spontaneous remission because they found no evidence it would differ across treatment arm. Even when equally applied, spontaneous remission would have led to a reduction in the cost and QALY differential between pegcetacoplan and the C5 inhibitors. However, the introduction of spontaneous remission is unlikely to have led to meaningful shifts in the economic results.
- The discontinuation rate for pegcetacoplan in the model was derived from the just the randomised control period of the PEGASUS study and was subject to adjustment based on differences between the study protocol and expected clinical practice. The company did not make use of the discontinuation data from the open label period of the study in the base case. However, alternative remission rates were explored in scenario analysis provided by the company and, as in the case of remission, alternative assumptions are unlikely to have led to meaningful changes in the economic results.

Despite these limitations, the economic case was demonstrated.

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

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 with PNH suffer from fatigue of varying levels. For many, the exhaustion is extremely debilitating leaving them unable to look after their own children, go to work or have a relationship. Severe headaches are also very common along with stomach pains and muscle aches. Patients often struggle to go out and, as a result, suffer from depression. A lack of self-worth and inability to socialise causes a deterioration

in mental state. The exhaustion and depression can lead to a lack of sex drive and erectile dysfunction, which can put a great strain on relationships.

- For the majority of PNH patients the C5 complement inhibitors have been excellent at giving a quality of life not previously possible. However, for some patients, the C5 complement inhibitor is not enough to stop haemolysis. These patients suffer from extreme fatigue and levels of anaemia requiring blood transfusions both of which make everyday tasks, work and family life difficult. Families and friends may have to take on the role of carers again, which can have negative psychological and physical impacts for them.

- Pegcetacoplan may be self-administered as a subcutaneous injection twice a week which offers a greater degree of freedom for patients and their families. Although less regular treatment would be preferred, patients with extravascular haemolysis cannot be adequately treated with the 2 weekly and 8 weekly C5 inhibitor infusions currently available.

Additional information: 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. Guidance for this service states that eculizumab is indicated for PNH patients fulfilling any of the following categories:[6]

- thrombosis related to PNH
- complications associated with haemolysis:
    1. renal failure
    2. pulmonary hypertension
- pregnancy (and for at least 3 months post-partum)
- haemolytic (LDH >1.5xULN) symptomatic PNH with either of the following:
    1. anaemia (Hb <9g/dL) or
    2. with agreement with Joint Service colleagues (multidisciplinary team)

Exceptional cases in whom eculizumab is considered appropriate (not fulfilling the above criteria) will be approved through discussion between the two nationally commissioned PNH Services and the National Commissioners.

The 2015 British Society of Haematology (BSH) guidelines for the diagnosis and management of adult aplastic anaemia (AA) includes a section on PNH and AA, which notes that allogeneic stem cell transplant has an inferior outcome in haemolytic and thrombotic PNH compared to best supportive care including eculizumab when indicated.[11] This guideline predates the availability of ravulizumab and pegcetacoplan.

Additional information: comparators

Ravulizumab and eculizumab (not recommended by SMC).

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
pegcetacoplan	1,080mg by subcutaneous infusion twice weekly	322,400

Costs from eMC Dictionary of Medicines and Devices Browser on 23 March 2022. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 12 patients eligible for treatment with pegcetacoplan in each year to which confidential estimates of treatment uptake were applied.

SMC is unable to publish the with PAS 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.**

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This assessment is based on data submitted by the applicant company up to and including 13 May 2022.

*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.