Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2305

ravulizumab 300mg/30mL concentrate for solution for infusion (Ultomiris®)

Alexion Pharma UK Ltd

15 January 2021

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

ADVICE: following a full submission under the orphan equivalent medicine process

ravulizumab (Ultomiris®) is accepted for restricted use within NHSScotland.

Indication under review: for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH):

- In patients with haemolysis with clinical symptom(s) indicative of high disease activity
- In patients who are clinically stable after having been treated with eculizumab for at least the past 6 months.

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

In two open-label, randomised, phase III studies, ravulizumab was non-inferior to another complement inhibitor across a range of relevant outcomes assessing the control of haemolysis.

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.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium

Indication

For the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH):

- In patients with haemolysis with clinical symptom(s) indicative of high disease activity
- In patients who are clinically stable after having been treated with eculizumab for at least the past 6 months.

Dosing Information

The recommended dosing regimen consists of a loading dose followed by maintenance dosing, administered by intravenous (IV) infusion every 8 weeks, starting 2 weeks after the loading dose. The doses of IV infusion are based on patient's body weight as detailed below:

- ≥40 to <60kg: 2,400mg loading dose and 3,000mg maintenance dose every 8 weeks.
- ≥60 to <100kg: 2,700mg loading dose and 3,300mg maintenance dose every 8 weeks.
- ≥100kg: 3,000mg loading dose and 3,600mg maintenance dose every 8 weeks.

For patients switching from eculizumab to ravulizumab, the loading dose of ravulizumab should be administered 2 weeks after the last eculizumab infusion. Treatment with ravulizumab is recommended to continue for the patient's lifetime, unless the discontinuation of ravulizumab is clinically indicated.

Ravulizumab must be administered by a healthcare professional and under the supervision of a physician experienced in the management patients with haematological or renal disorders.

Refer to the summary of product characteristics for further details.[1]

Product availability date

February 2021.
Ravulizumab meets SMC orphan equivalent criteria.

Summary of evidence on comparative efficacy

Paroxysmal nocturnal haemoglobinuria (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 terminal complement inhibitor proteins on cell surfaces. Their absence in blood cells results in uncontrolled complement activation and systemic complications which include chronic intravascular haemolysis, impaired bone marrow function and thrombosis. Thromboembolic events are the leading cause of death in patients with PNH. Ravulizumab is a monoclonal antibody that binds to the complement protein C5 inhibiting the cleavage to C5a (the pro-inflammatory anaphylatoxin) and C5b (the initiating subunit of the terminal complement complex C5b-9).

Ravulizumab was designed by substituting four amino acids in the backbone of eculizumab which results in an increased antibody half-life, allowing administration once every 8 weeks.[1, 2]

The clinical evidence comes from two open-label, randomised, phase III, non-inferiority studies which compared ravulizumab with eculizumab in patients with a documented diagnosis of PNH. Both studies comprised a 4-week screening period, a 26-week randomised treatment period and an open-label extension period of up to 2 years.[2-4]

Study 301 enrolled 246 eculizumab-naive patients who had active haemolysis (lactate dehydrogenase [LDH] ≥1.5 times the upper limit of normal [ULN]) and at least one PNH-related sign or symptoms from fatigue, haemoglobinuria, abdominal pain, dyspnoea, anaemia [haemoglobin <10g/dL], history of major adverse vascular event [MAVE, including thrombosis], dysphagia, erectile dysfunction or history of packed red blood cell [RBC] transfusion due to PNH in the previous 3 months. Eligible patients were randomised equally to ravulizumab by intravenous (IV) infusion at a loading dose and maintenance dose according to weight as detailed in the dosing section or eculizumab induction with 600mg IV infusion on days 1, 8, 15 and 22 and maintenance of 900mg on day 29 and then every 2 weeks. Randomisation was stratified by transfusion history (0, 1 to 14 or >14 units of packed RBC in the previous year) and by LDH levels at screening (1.5 to <3 times ULN or ≥3 times ULN).

Study 301 had two co-primary outcomes which were assessed in the full analysis set (FAS; all patients who received at least one dose of study medicine and had at least one efficacy assessment):

- Transfusion avoidance (defined as the proportion of patients who remained transfusion-free and did not require a transfusion according to the following protocol guidelines: haemoglobin ≤9g/dL with anaemia-related signs or symptoms of severity enough to warrant transfusion or haemoglobin ≤7g/dL regardless of presence of clinical symptoms) through to week 26; and
- Haemolysis, measured by the proportion of patients with LDH normalisation (ULN of 246 units/L) from day 29 to week 26.[2, 4]

Study 302 enrolled 195 patients who were clinically stable (LDH level <2 x ULN and no MAVE in previous 6 months and LDH ≤1.5 x ULN at screening) after receiving eculizumab for ≥6 months previously. Eligible patients were randomised equally to receive ravulizumab (at dose for Study 301) or eculizumab 900mg by IV infusion every 2 weeks. Randomisation was stratified by transfusion history (receipt of packed RBC in the previous year: yes/no). The primary outcome in Study 302 was haemolysis, measured by the percentage change in LDH levels from baseline to week 26, assessed in the FAS which included all patients who received at least one dose of study medication and had at least one efficacy assessment.[2, 3]

In both studies, ravulizumab was non-inferior to eculizumab in the primary outcomes at the pre-defined margins and details are presented in table 1 below:

Table 1: Non-inferiority results for the primary outcomes of Study 301 and 302.[2, 4]

Primary outcome	Ravulizumab	Eculizumab	Difference or Odds ratio (95% CI)	Non-inferiority margin
Study 301	**n=125**	**n=121**		
Transfusion avoidance rate	74%	66%	Difference: 6.8% (-4.7 to 18)	-20%
LDH normalisation	54%	49%	Odds ratio: 1.19 (0.80 to 1.77)	0.39
Study 302	**n=97**	**n=98**		
Change in LDH, LS mean, %	-0.8%	8.4%	Difference: 9.2% (-0.4 to 19)	-15%

LDH=lactate dehydrogenase; CI=confidence interval; LS=least square

Following the hierarchical statistical testing strategy in both studies, since non-inferiority was demonstrated for the primary outcomes, the key secondary outcomes were tested for non-inferiority. The order varied between studies but all key secondary outcomes were found to be non-inferior in the ravulizumab group compared with the eculizumab group. Since all outcomes were non-inferior, then superiority of secondary outcomes was tested. However, the first outcome tested for superiority in each study (breakthrough haemolysis in Study 301 and percentage change in LDH in Study 302) failed to reach statistical significance and further statistical testing was not performed (any results reported for these outcomes are descriptive only and not inferential; no p-values reported).[2, 4]

Table 2: Results of non-inferiority testing of key secondary outcomes in Study 301 and 302[2-4]

	Study 301		Study 302	
Outcome	**Ravulizumab (n=125)**	**Eculizumab (n=121)**	**Ravulizumab (n=97)**	**Eculizumab (n=98)**
Change in LDH, LS mean, %	-77%	-76%	-	-
Difference (95% CI)	0.8% (-3.6 to 5.2)		-	
Change in FACIT-Fatigue score, LS mean	7.07	6.40	2.0	0.54
Difference (95% CI)	0.67 (-1.21 to 2.55)		1.5 (-0.2 to 3.2)	
Breakthrough haemolysis rate, %	4.0%	11%	0%	5.1%
Difference (95% CI)	6.7% (-0.2 to 14)		5.1% (-8.9 to 19)	
Haemoglobin stabilisation rate, %	68%	64%	76%	76%
Difference (95% CI)	2.9% (-8.8 to 15)		1.4% (-10 to 13)	
Transfusion avoidance, %[A]	-	-	88%	83%

Difference (95% CI)	-	5.5% (-4.3 to 16)

[A] transfusion avoidance was a co-primary outcome in Study 301

LDH=lactate dehydrogenase; CI=confidence interval; LS=least square; FACIT=Functional Assessment of Chronic Illness Therapy. Haemoglobin stabilisation defined as defined as avoidance of a ≥2g/dL decrease in haemoglobin level from baseline in the absence of a transfusion. Breakthrough haemolysis defined as at least one new or worsening sign or symptom of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, dyspnoea, anaemia [haemoglobin <10g/dL]), MAVE (including thrombosis), dysphagia, or erectile dysfunction) in the presence of LDH ≥2 x ULN after prior reduction of LDH to <1.5 ULN during treatment.

Quality of life was assessed using the FACIT-Fatigue scale (results are presented in table 2) and by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Scale (EORTC QLQ-C30) version 3.0 (range 0 to 100, with higher scores indicating better quality of life). A mean improvement in EORTC QLQ-C30 global health status from baseline was reported in ravulizumab patients and eculizumab patients of 13.2 versus 12.9 in Study 301 and of 1.15 versus -1.93 in Study 302.[2-4]

Patients who completed the 26-week treatment phase of both studies could enter the open-label extension when all patients received ravulizumab for up to 2 years. Limited results to week 52 have indicated that the treatment effect of ravulizumab was maintained and was similar in patients who switched from eculizumab at week 26.[5, 6]

A subset of patients from the extension of Study 302 completed a survey of patient preference. Ninety-five of 98 enrolled patients completed the 11-item PNH patient preference questionnaire: 50 patients originally randomised to ravulizumab and 45 patients randomised to eculizumab and switched to ravulizumab at week 26. A higher proportion of patients reported a preference for ravulizumab (93%) compared with no preference (6%) or eculizumab (1%). The most important factor in deciding preference was the frequency of infusions in 43% of patients and overall quality of life in 23%.[7]

Summary of evidence on comparative safety

The safety profile, including that of adverse events of special interest (infections and infusion reactions) was similar with ravulizumab and eculizumab, although long-term comparative safety data are limited to 26 weeks. As with eculizumab, treated patients are at increased risk of meningococcal infections and patients must be vaccinated against this before treatment.[2, 8]

In Study 301, a treatment-emergent adverse event was reported by 88% (110/125) of patients in the ravulizumab group and 87% (105/121) of patients in the eculizumab group and these were considered treatment-related in 41% of patients in both groups. In the ravulizumab and eculizumab groups respectively, patients reporting a serious adverse event were 8.8% versus 7.4%, which were considered treatment-related in 3.2% and 0.8% of patients respectively. Only one patient (0.8%) in the eculizumab group discontinued study medication due to an adverse event. The most frequently reported treatment-emergent adverse events in the ravulizumab and eculizumab groups respectively were: headache (36% versus 33%), upper respiratory tract

infection (10% versus 5.8%) and nasopharyngitis (8.8% versus 15%). A MAVE was reported in two ravulizumab patients (1.6%) and one eculizumab patient (0.8%).[2, 4]

In the Study 302, a treatment-emergent adverse event was reported by 88% (85/97) of patients in the ravulizumab group and 88% (86/98) of patients in the eculizumab group and these were considered treatment-related in 25% and 14% respectively, mainly due to a higher incidence of headache (12% versus 4.1%). In the ravulizumab and eculizumab groups respectively, patients reporting a serious adverse event were 4.1% versus 8.2%, which were considered treatment-related in 1.0% of each group. No patients in either group discontinued study medication due to an adverse event. The most frequently reported treatment-emergent adverse events in the ravulizumab and eculizumab groups respectively were: headache (27% versus 17%), nasopharyngitis (22% versus 20%) and upper respiratory tract infection (19% versus 10%). No MAVE was reported in either treatment group.[2, 3]

Summary of clinical effectiveness issues

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 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. In Scotland, patients with PNH are managed by the PNH National Service in England in consultation with their local haematologist. Eculizumab was the only treatment with a marketing authorisation for the treatment of PNH, it is not recommended for use by SMC (SMC 1130/16). The PNH National Service has indications for treatment with eculizumab which are detailed in the guidelines section below and patients in Scotland who are eligible for treatment currently receive eculizumab under the direction of the PNH National Service.[9] Ravulizumab is structurally similar to eculizumab but has an increased antibody half-life, which would reduce the burden of administration from every 2 weeks to every 8 weeks during maintenance.[1, 8]

The key studies found that ravulizumab was non-inferior to the comparator, eculizumab, for all primary and key secondary outcomes in PNH patients with active haemolytic, symptomatic disease who had not received eculizumab and in PNH patients who were clinically stable in ≥6 months of previous eculizumab treatment. The company notes that, in a small number of patients in clinical practice, the dose of eculizumab is increased above the licensed dose to reduce the incidence of breakthrough haemolysis. The company suggests that the use of ravulizumab may fill an unmet need in reducing breakthrough haemolysis in these patients. However no significant benefits were demonstrated in the key studies, including reduced incidence of breakthrough haemolysis with ravulizumab compared with eculizumab,.[2-4]

Both studies were of open-label design, which was considered acceptable by the European Medicines Agency (EMA) due to the different dosing regimens for study medicines. To minimise potential bias, the assessment of haemolysis according to LDH levels was made by laboratory staff unaware of study treatment. In addition, the need for transfusion was determined by strict

protocol. However, the open-label design may affect subjective assessments of quality of life and safety.

The primary analyses of both studies assessed non-inferiority in the FAS but analyses in the per protocol population are preferred for assessing non-inferiority. In both studies, the primary analyses in the FAS was supported by sensitivity analysis in the per protocol populations which found similar results.[2]

The duration of the randomised, treatment period of both studies was 26 weeks, which although acceptable to the EMA, is short for a treatment intended for life-long use. In patients randomised to ravulizumab, 26 weeks of study treatment only comprised a loading dose plus three doses of maintenance treatment. There are no longer term comparative efficacy or safety data but the treatment effect of ravulizumab appears to be maintained to 52 weeks in the available results of the open-label extensions. A significant proportion of patients in Study 301 and Study 302 (52% and 22% respectively) were Asian and results from these patients may be less generalisable to patients in Scotland.[2-4]

In clinical practice, treatment of PNH patients is managed by the PNH National Service and eculizumab is used under specifically defined indications. Study 301 enrolled patients who had haemolytic (LDH ≥1.5 x ULN) symptomatic PNH, which is covered by the indications specified by the PNH National Service but the definitions of symptomatic disease may be wider than indicated by the PNH National Service.[2-4, 9] The PNH National Service notes that in practice a higher dose of eculizumab (1,200mg) than that licensed may be required for some patients and there is currently no evidence on the comparative efficacy and safety of ravulizumab versus this higher dose of eculizumab. A small, treatment switching, phase IV study is planned.[9, 10]

The introduction of ravulizumab would offer an alternative treatment option to eculizumab. The dosing regimen for ravulizumab (loading dose followed by IV infusions every 8 weeks) is less burdensome than for eculizumab (4-week initial weekly dosing followed by dosing every 2 weeks) and this may offer advantages for the patient and service. Ravulizumab has been shown to be as effective as the licensed dose of eculizumab but statistically significant differences between the treatments have not been found. Ravulizumab is only licensed for the treatment of PNH in adult patients aged ≥18 years, while eculizumab is licensed for treatment in adults and children weighing >5kg.[1, 8]

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of ravulizumab, as an orphan-equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- PNH is a rare, incurable, acquired, chronic disorder of haemolysis, which can have a devastating effect on patients and their families. Patients experience debilitating

symptoms of fatigue, difficulty swallowing, erectile dysfunction, abdominal pain and the risk of life-threatening hemolysis, all of which can limit the ability to function on a daily basis.

- The current treatment, eculizumab, is effective but is given by intravenous infusion every two weeks. Ravulizumab is administered every 8 weeks and reduces the burden of treatment on patients and their families. Less interference may improve the quality of normal family and work life and allow planning of future events and travel.
- Ravulizumab is as effective as eculizumab. There may be some patients who develop breakthrough haemolysis during eculizumab treatment, switching to ravulizumab could have a profound effect on controlling symptoms. The PACE participants described this effect as transformational, it may allow patients to forget they have this condition. This may have a substantial physical and psychological impact on quality of life for patients and their families.
- The reduction in annual infusions from 24 with eculizumab to six or seven with ravulizumab may also reduce scarring of veins, allow affected veins to heal and avoid the need for cannulation devices.

Additional Patient and Carer Involvement

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. A representative from PNH Scotland participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company presented an economic analysis evaluating the cost-effectiveness of ravulizumab within its licensed indication, with an additional restriction to align with the eligibility criteria stipulated for eculizumab use in NHS England's service specification for PNH. Ravulizumab was compared against eculizumab alone.

The submission primarily focused on a cost-minimisation analysis, with a supplementary cost-utility analysis (CUA) provided. The cost-minimisation analysis assumed no difference in clinical effectiveness between ravulizumab and eculizumab, and was a simple comparison of acquisition and administration costs. The CUA was more complex, using a state transition model covering 10 health states, representing different categories of breakthrough haemolysis (Complement-amplifying-condition associated and incomplete C5 inhibition-related), as well as modelling history of previous breakthrough haemolysis (BTH) events. Two states were applied which assumed patients required an increased dose of eculizumab for the remainder of the time horizon, following two incomplete C5 inhibition-related BTH events. Background mortality was assumed constant with the general population, and spontaneous remission and PNH-specific mortality were only modelled in scenario analyses. No treatment waning effect was applied for either eculizumab

or ravulizumab. A lifetime horizon of 50 years was applied, and a perspective of NHS and social services was used in both the CUA and cost-minimisation analysis.

The justification for the cost-minimisation analysis is based on non-inferiority to eculizumab demonstrated in the ALXN1210-PNH-301 and ALXN1210-PNH-302 trials. The cost-utility analysis made use of independent patient-level data from the same trials, to apply point estimates which imply numerical improvements for ravulizumab in terms of the probability of various BTH events as well as differences in the probability of transfusions and the amount of blood units required. Utilities were estimated through the use of a mapping algorithm to translate EORTC-QLQ-C30 data into EQ-5D, resulting in baseline ('no BTH') utilities of 0.79 and 0.85 for eculizumab and ravulizumab respectively.[11] The difference in baseline utility was due to a 0.057 utility increment for the reduced dosing frequency of ravulizumab, derived through a discrete choice experiment. Further disutilities were estimated for specific BTH-related events, and no adverse event disutilities were applied.

Costs included medicines acquisition and administration costs, costs of meningococcal vaccination and prophylactic antibodies, and costs of transfusion, hospitalisation and consultant follow-up (for the CUA only).

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. The cost per pack of ravulizumab was applied at a list price of £4,533 per 300mg and a list price of eculizumab of £3,150 per 300mg.

The base case results of the cost-minimisation analysis are shown in Table 3. SMC would wish to present the with-PAS cost-minimisation results that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented for the cost- minimisation analysis.

Table 3: Base case results, cost-minimisation analysis – (list price)

Costs	**Eculizumab**	**Ravulizumab**
Incremental costs (list price)		£1,470,784

The results of the supplementary cost-utility analysis are presented in Table 4 at PAS prices. The predominant driver of QALY gains is the utility increment from reduced dosing frequency, while the cost saving is achieved from a proportion of patients being assumed to initiate and remain on the higher-than-licensed dose of eculizumab 1200mg for a lifetime.

Table 4: Cost-utility analysis – base case results (PAS price)

Technologies	**Incremental QALYs**	**ICER (PAS price)**
Eculizumab	-	Dominant
Ravulizumab	0.97	
Key: PAS, Patient Access Scheme; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio		

A number of key scenarios were obtained for the cost-minimisation (Table 5) and cost-utility analysis (Table 6), and were considered to be more clinically plausible by NDC.

Table 5: Key cost-minimisation scenarios

		Scenario analysis assumption	**Incremental costs (list price)**
	Base case		£1,470,784
1.	Time Horizon (50 years)	10	£654,343
2.	Spontaneous remission rate (0)	0.001	£1,067,910

Table 6: Cost-utility analysis scenarios

	Scenario*	**Scenario**	**Incremental QALYs**	**ICER (PAS price)**
	Base case		0.97	Dominant
1.	Utility increment of ravulizumab vs eculizumab (0.0570)	0.025	0.45	Dominant
2.	Spontaneous remission rate (0.00)	0.0010	0.71	Dominant
3.	Comparative effectiveness (Numerical benefit assumed for ravulizumab)	Clinical equivalence to eculizumab 900mg	0.97	Dominant
4.	Combined analysis	Scenarios 1,2 and 3	0.32	Dominant
*base case values shown in brackets				

There are a number of important limitations to the analyses:

- Although used in clinical practice and therefore an appropriate comparator for the economic analysis, eculizumab is not recommended by SMC. The New Drugs Committee was of the view that a comparison against best supportive care could have been considered. The submitting company did not provide this comparison on the grounds that all patients meeting the eligibility criteria for ravulizumab will currently be eligible for, and will receive, eculizumab.
- The approach to the cost-minimisation analysis requires an assumption of clinical equivalence of ravulizumab to both eculizumab 900mg and eculizumab 1200mg. Given that

ravulizumab demonstrated non-inferiority to eculizumab 900mg, this aspect of the assumption is likely appropriate. However, no evidence exists to suggest that ravulizumab is equivalent to the higher dose, and the decision to escalate dose implies there will be clinical benefit to be gained for eculizumab 1200mg. Given the very high acquisition cost of eculizumab, addition of these extra costs while assuming no additional benefit for the comparator is likely to bias the results in favour of ravulizumab. A simple cost comparison against the licensed dose is preferred, and was provided as a scenario analysis.

- The time horizon selected is potentially too long for a population with a life-limiting condition. The use of a ten year time horizon was provided and demonstrates the sensitivity to the use of shorter time horizons (Table 5, Scenario 1).

The limitations to the cost-utility analysis include:

- The use of point estimates from the clinical trial within the economic model assumes superiority of ravulizumab to eculizumab 900mg. This ignores the wide 95% confidence intervals observed for each parameter, which under formal statistical testing did not meet the criteria for statistical significance. An assumption of clinical equivalence to eculizumab 900mg, whilst acknowledging a degree of benefit due to reduced dosing frequency, was deemed more appropriate (Table 6, Scenario 3).
- The assumption of a quality of life advantage arising from patient preference for the reduced dosing frequency of ravulizumab is appropriate, however, the extent of benefit is higher than reported in similar previous research. Using a utility increment in line with previous estimates (0.025) results in a halving of the QALY gain associated with ravulizumab (Table 6, Scenario 1).
- The omission of spontaneous remission rates may be inappropriate. Although uncertain, the occurrence of spontaneous remission appears to reduce the cost savings relative to eculizumab between a range of one-third to one-half those estimated in the base case analysis (Table 6, Scenario 2). This would be amplified when only comparing against the licensed dose.
- A plausible combined analysis assuming equivalent clinical effects, application of the lower utility gain for dosing frequency, and inclusion of spontaneous remission rates results in a substantial increase in the ICER (Table 6, Scenario 4).

The Committee considered the benefits of ravulizumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as ravulizumab is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted ravulizumab for restricted use in NHSScotland.

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

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:

- 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 <90g/L) 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.[9]

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.[12] This guideline predates the availability of ravulizumab.

Additional information: comparators

Eculizumab as indicated by the PNH National Service.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
ravulizumab	2,700mg loading dose by IV infusion, then 3,300mg by IV infusion 2 weeks later and every 8 weeks	389,838 for year 1 299,178 to 349,041 for subsequent years

Cost from company submission. Costs calculated for adult weighing 70kg (relevant to weight band ≥60 to <100kg). Costs do not take patient access schemes into consideration.

Additional information: budget impact

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.

*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 November 2020.

**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: http://www.scottishmedicines.org.uk/About_SMC/Policy*

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.