Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Jonathan G Fox

eculizumab 300mg/30mL vial concentrate for solution for infusion (Soliris®)

SMC No. (1130/16)

Alexion Pharma UK

04 March 2016

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 Scotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the ultra orphan process

eculizumab (Soliris®) is not recommended for use within NHS Scotland.

Indication under review: In adults and children, for the treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH). Evidence of clinical benefit is demonstrated in patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history.

In a controlled study in patients with transfusion-dependent PNH, eculizumab reduced the rate of haemolysis and improved anaemia compared with placebo. Observational data from a subset of the PNH registry suggest that these benefits may also be achieved in patients with no history of transfusions. Uncontrolled data suggest that eculizumab reduces the incidence of thrombosis in patients with PNH.

The submitting company did not present a sufficiently robust economic analysis and in addition their justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC.

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

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 11 April 2016

Indication

In adults and children, for the treatment of patients with paroxysmal nocturnal haemoglobinuria. Evidence of clinical benefit is demonstrated in patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history.

Dosing Information

In adult patients (≥18 years of age) there is a 4-week initial phase followed by a maintenance phase:

- Initial phase: 600mg by intravenous (IV) infusion (25 to 45 minutes) every week for the first four weeks.
- Maintenance phase: 900mg by IV infusion (25 to 45 minutes) for the fifth week followed by 900mg by IV infusion (25 to 45 minutes) every 14 ± 2 days.

Paediatric patients with body weight ≥40kg are treated with the adult dosing recommendations; for paediatric patients with body weight below 40kg, please see dosing regimen in the current SPC.

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

Product availability date

April 2015. Eculizumab has been designated an orphan medicine by the European Medicines Agency and also meets SMC ultra orphan criteria.

Summary of evidence on comparative efficacy

Paroxysmal nocturnal haemoglobinuria (PNH) is a haematopoietic stem cell disorder with an estimated prevalence of 13 cases per million. It is an acquired clonal genetic disease caused by a somatic mutation in the gene PIG-A in the X-chromosome, resulting in a deficiency of the glycosyl phosphatidylinositol (GPI)-anchored complement regulatory proteins CD55 and CD59. The proportion of red blood cells (RBCs) affected by PNH varies among patients and over time in an individual patient. Deficiency of CD55 and CD59 renders PNH RBCs sensitive to complement-mediated intravascular haemolysis leading to haemolytic anaemia, thrombosis and deficient haematopoiesis. Median survival from initial diagnosis is 15 years. Eculizumab is a humanised recombinant monoclonal antibody that binds to the human C5 complement protein and inhibits its cleavage to C5a and C5b, preventing the final stage of complement activation and thereby blocking complement-mediated cell lysis and activation.[1]

Eculizumab was initially licensed in 2007 for a narrower PNH population as the evidence of its clinical benefit was limited to adults with a history of transfusions. Since then, the indication has been extended twice; firstly to include children and, subsequently, to include patients without a history of transfusions.

As eculizumab for PNH is an ultra orphan medicine, its evidence base is limited. The only controlled study data are from a phase III study (TRIUMPH) which provided evidence for the

initial regulatory approval of eculizumab in transfusion-dependent adults with PNH.[2] The submitting company has also presented uncontrolled data from an open-label, phase III study (SHEPHERD),[3] a phase III extension study (E05-001)[4,5] that included patients from TRIUMPH and SHEPHERD, a small paediatric study (M07-005)[6,7] and PNH registry data (M07-001).[1]

TRIUMPH was a 26-week, phase III, placebo-controlled, randomised study in 87 patients with PNH.[2] Eligible patients were aged ≥18 years with ≥10% PNH type III erythrocytes and platelet counts of ≥100x10^9/L, lactate dehydrogenase (LDH) levels ≥1.5 times the upper limit of normal (ULN) and having received ≥4 transfusions in the previous 12 months. After a 2-week screening period, eligible patients entered a 13-week observation period during which they were given a RBC transfusion if they had a haemoglobin level ≤90g/L with symptoms, or ≤70g/L with or without symptoms. This served as the haemoglobin set point for the individual patient for the rest of the study.[2,8] Patients were randomised in a ratio of 1:1 to receive eculizumab (licensed dose) or placebo for 26 weeks, with stratification by the number of units of RBCs transfused during the previous year. Patients could continue to receive stable doses of epoetin, immunosuppressives, corticosteroids, coumarins, low-molecular-weight heparins, iron supplements and folic acid. All patients were vaccinated against *Neisseria meningitidis*.[2,6,8]

There were two primary endpoints: stabilisation of haemoglobin (defined as a haemoglobin value maintained above the set point in the absence of transfusions) and median number of RBC units transfused. These endpoints were assessed in the intention to treat (ITT) population (all randomised patients). After 26 weeks of treatment, stabilisation of haemoglobin was achieved in significantly more eculizumab-treated patients than placebo-treated patients: 49% (21/43) versus zero (0/44) ($p<0.001$). The median number of RBC units transfused was significantly reduced in the eculizumab group (0 [range 0 to 16]) versus placebo (10 [range 2 to 21]) after 26 weeks; corresponding six-month pre-study values were 9.0 and 8.5 units respectively.[2] Secondary endpoints included transfusion independence, which was achieved by 51% (22/43) eculizumab- and zero (0/44) placebo-treated patients. Haemolysis, as measured by LDH area under the curve (AUC) from baseline, was significantly reduced by 86% in the eculizumab group compared with the placebo group (58,587 versus 411,822 U/L x day). The mean LDH level decreased from a baseline of 2,200 U/L to 327 U/L at week 26 in the eculizumab group and remained high in the placebo group (2,258 U/L and 2,419 U/L respectively). Changes in the functional assessment of chronic illness therapy fatigue (FACIT-fatigue) score were significantly improved in the eculizumab group compared with placebo: difference of 10.4 points (≥4 points is considered minimally important).[2,8]

SHEPHERD was a supportive, open-label, uncontrolled study; 97 adult patients with PNH, platelet count of ≥30 x 10^9/L and a lower baseline transfusion requirement than for TRIUMPH (≥one transfusion in the past 2 years), received eculizumab for 52 weeks.[3] The primary outcome of haemolysis, assessed by LDH AUC, was significantly reduced after 52 weeks of eculizumab therapy, with a median change of -632,264 U/L x day. There were significant differences in secondary outcomes, including LDH changes from baseline and associated increases in the proportion of PNH type III RBC and haemoglobin levels. Transfusion requirements reduced to a median of zero units per patient during the 52 week study period and 51% (49/97) patients did not require any transfusions.[3]

E05-001 was an open-label extension study that included 187 of a possible 195 patients from the TRIUMPH and SHEPHERD studies plus one small pilot study.[4,5] Patients were treated with the licensed maintenance dose of eculizumab and assessed after 36 months of treatment across the core and extension studies in the ITT population. The rate of thrombosis was compared for the pre-eculizumab and the eculizumab treatment periods and reduced from 7.37

events per 100 patient-years (124 events over 1,683 patient years) before eculizumab treatment to 2.14 events per 100 patient-years (10 total events over 467 patient years) during eculizumab treatment. The percentage of patients with thromboembolic events decreased from 32% (63/195) before treatment to 3.6% (7/195) during treatment. A time-matched analysis of two periods of 467 patient years, before and after eculizumab treatment, showed that the rate of thrombosis was reduced from 11.13 events per 100 patient years to 2.14 events per 100 patient years, a relative reduction of 82% ($p<0.0005$).[5] Four patients died during the study, corresponding to a three year estimated overall survival of 98%. None of the deaths were considered to be treatment-related, At 36 months, LDH levels were reduced by a median of 87%; renal function was stable or improved in 93% of patients and there was a 55% reduction in RBC units transfused. The percentage of patients achieving transfusion independence was 82% (64/78) by the last six months of treatment, compared with only 8.2% (16/195) in the six months before the start of treatment.[4,5]

M07-001 was a prospective, observational, non-interventional study using PNH registry data.[1] Patients could enrol if they had been diagnosed with PNH or had a detectable granulocyte PNH clone regardless of disease severity or prior treatments. Patients eligible for the analysis had no history of transfusions, could have initiated treatment with eculizumab after PNH Registry enrolment or had no prior treatment with eculizumab, and had granulocyte clone size ≥1%. In addition, patients had to have a baseline LDH of ≥1.5xULN. From the subset of 189 out of 1,547 registry patients that fulfilled these criteria, 24% (45/189) began treatment with eculizumab after entry into the registry. Compared with the 144 patients in the subset who did not receive eculizumab, the following results were observed after six months follow up: a clinically meaningful decrease in the primary outcome of LDH (-1,042 U/L [range -4,215 to 597]); an improvement of scores reflecting fatigue (FACIT-fatigue score: +8 [range -8 to 32]; European Organisation for Research and Treatment of Cancer (EORTC)-fatigue score: -22 [range -67 to 11]) and an increase in haemoglobin level from 100 to 113g/L.[1]

M07-005 was an uncontrolled, open label study of 12 weeks treatment with eculizumab in seven paediatric patients (four girls and three boys) with PNH.[6,7] Patients were 11 to 17 years of age (median age: 15.6 years) and had a median weight of 57.2kg (range of 48.6 to 69.8kg).[6] Baseline plasma levels of free haemoglobin were ≥ULN (6.9mg/dL) for all patients with the exception of one patient who had normal baseline levels. Patients had to have >5% GPI-deficient RBC or granulocytes as confirmed by flow cytometry, evidence of haemolytic anaemia as documented by LDH >ULN or at least one transfusion in the past two years for anaemia or anaemia-related symptoms. All patients had to be vaccinated against *Neisseria meningitidis*, *pneumococcus* and *haemophilus*.[7] Treatment with eculizumab at the proposed child dosing regimen was associated with decreased intravascular haemolysis as measured by serum LDH level. It also produced a marked reduction in blood transfusions and a trend towards an overall improvement in general function.[6]

A further supportive observational study involving 79 patients in the UK who had been treated with eculizumab for a mean duration of 39 months (range, 1-98 months) indicated no difference in mortality when compared to age and sex matched controls ($p=0.48$). Observational data indicate that eculizumab may improve survival to a similar level to that of the general population.[9]

Summary of evidence on comparative safety

In the TRIUMPH study the most frequently reported adverse events in the eculizumab versus placebo groups were headache (44% versus 27%), nasopharyngitis (23% versus 18%), back pain (19% versus 9%), nausea (16% versus 11%) and fatigue (12% versus 2%). There were no significant differences between the two groups in the incidence of any adverse event. After two weeks of treatment, the incidence of headache was similar in the two groups. Serious adverse events were reported in 13 patients (four in the eculizumab group and nine in the placebo group) but none was considered to be related to treatment. One patient in the placebo group experienced a thrombosis.[2] The E05-001 extension study found that eculizumab was well tolerated, with no evidence of cumulative toxicity.[5] In children and adolescent PNH patients (aged 11 years to less than 18 years) included in M07-005, the safety profile appeared similar to that observed in adult PNH patients. The most common adverse reaction reported in paediatric patients was headache.[6]

Eculizumab, through its mechanism of action, increases susceptibility to severe infections including meningococcal infection (*Neisseria meningitidis*). All patients must be vaccinated against meningococcal infection at least 14 days before they begin eculizumab treatment and re-vaccinated according to current guidelines. Vaccination may not be sufficient to prevent meningococcal infection and all patients should be monitored for early signs of meningococcal infection. Cases of serious or fatal meningococcal infections have been reported in eculizumab-treated patients. Physicians should discuss the benefits and risks of eculizumab therapy with patients and provide them with a patient information brochure and a patient safety card.[6] Patients under 18 years of age must also be vaccinated against *Haemophilus influenzae* and pneumococcal infections.[6]

There is a possibility of serious rebound haemolysis on discontinuation/interruption and patients should be monitored for signs of serious haemolysis and other reactions for at least eight weeks after discontinuation. Thrombotic events were observed in 16% (3/19) of patients who discontinued treatment with eculizumab, all within eight weeks of taking their last dose.[5]

Safety issues are being monitored as part of a risk management plan which includes the PNH global registry.[6]

Summary of clinical effectiveness issues

PNH is a progressive, debilitating disease with high levels of mortality. Without treatment, the median survival from initial diagnosis is 10-15 years. Common clinical manifestations are haemolytic anaemia, venous thrombosis and bone marrow failure. Excessive levels of cell-free plasma haemoglobin during intravascular haemolysis contribute to platelet activation, pro-coagulant activity and thromboembolism, which is the leading cause of mortality in these patients.[1] If patients have few or no symptoms, treatment with folic acid and possibly iron may suffice. Patients with acute thrombosis are often treated with thrombolytic therapy, long-term anticoagulants and antiplatelets. Transfusions improve anaemia and also help reduce the production of RBC in the bone marrow during periods of sustained haemoglobinuria.[1] Allogeneic bone marrow transplantation is the only curative therapy but its use is limited to patients with severe PNH (life-threatening thrombosis or dangerously low blood counts) as it carries a high

(15 to 20%) mortality risk.[1] In addition, this procedure is not possible for most patients due to lack of a suitable donor. The UK has a National PNH service led by two centres: St James' University Hospital, Leeds and King's College Hospital, London. Patients from Scotland are affiliated with the Leeds centre. Eculizumab is the first and only medicine to be licensed for PNH and offers a therapeutic option beyond management with supportive care. Current patient selection criteria used by clinicians in the UK are listed in the Additional information – guidelines and protocols section of this document. Eculizumab for the treatment of PNH meets SMC ultra orphan criteria.

Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, namely routine availability of an effective treatment for severely symptomatic PNH.

The benefit of eculizumab in significantly reducing haemolysis, anaemia and fatigue, and in improving quality of life has previously been demonstrated in transfusion-dependent adults with PNH in the TRIUMPH study.[2] The open-label 52-week SHEPHERD study included patients with minimal transfusion needs and provided supportive evidence.[3] Uncontrolled data from the E05-001 extension study, in adults who have received prior transfusions, suggest that the rate of thrombosis is reduced with eculizumab when compared with the rate observed before treatment. There were also indications of improvement in haemolysis, renal function and transfusion dependence.[4,5] Observational data from a subset of PNH registry patients with no history of transfusions suggest that treatment with eculizumab reduces haemolysis and associated symptoms such as fatigue and anaemia, compared with the 144 patients in the subset who did not receive eculizumab.[1] Observational data indicate that eculizumab may improve survival to a similar level to that of the general population.[9]

Limitations of the evidence include the absence of controlled data on the safety and efficacy of eculizumab in patients who are not dependent on transfusions. The evidence for extending the indication to include patients without a history of transfusions was, of necessity, based on data from the Global PNH Registry, although assessments were not blinded and some evaluations were missing.[1] The European Medicines Agency designated the PNH registry study as the main study providing evidence for the extension of the licensed indication to include patients who were not dependent on transfusions. The Registry data suggest that treatment with eculizumab may improve the condition of the patients without recent history of transfusion and who present signs of severity of PNH. Whilst observational and uncontrolled data exist, there are no randomised, controlled data on the effect of eculizumab on overall survival or on the rate of thrombosis, one of the serious consequences of PNH and the leading cause of death in patients. The evidence for the use of eculizumab in children is from one uncontrolled study (M07-005) in seven children which suggested that eculizumab provided clinical benefit. However there is no study evidence in children under 11 years or in those weighing less than 48kg.[7]

The Cochrane Collaboration conducted a review of the use of eculizumab in PNH which was published in 2014. The authors noted the lack of evidence versus placebo in terms of overall survival, nonfatal thrombotic events, transformation to myelodysplastic syndrome and acute myelogenous leukaemia, and development and recurrence of aplastic anaemia on treatment. However, they accepted that current evidence indicates an increase in health-related quality of life and transfusion independence.[10]

Clinical experts consulted by SMC considered that eculizumab is a significant therapeutic advancement as it is the only effective treatment for PNH, reducing thrombotic risk, improving

symptoms and quality of life and potentially improving survival. They advise that patients should be treated with eculizumab according to the criteria used by the National PNH service.

The submitting company has advised that it funds a Healthcare-at-Home service which involves a visit by a nurse to administer the medicine and monitor the patient post-dose.

Summary of patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with a patient group representative and clinical specialists was held to consider the added value of eculizumab, as an ultra-orphan medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- PNH is a rare, acquired, chronic disorder of haemolysis which can have a devastating effect on patients and their families. Patients experience symptoms of fatigue, difficulty swallowing, erectile dysfunction and abdominal pain, all of which can be severe and limit the ability to function on a daily basis. End organ damage can occur leading to thrombosis, pulmonary hypertension and renal dysfunction. Median survival with conventional therapy is 10-15 years from diagnosis.

- Conventional management (regular blood transfusion and use of anticoagulants) does not address the underlying cause of the disease and clinicians indicated that it has limited evidence of efficacy.

- Experience with eculizumab has shown a dramatic impact on patient fatigue and health-related quality of life, as well as the potential to improve survival to a level comparable with the general population[9]. PACE participants described eculizumab as 'transformational' in the way it was able to give patients their life back, and highlighted the psychological benefit associated with a substantially reduced risk of thrombosis.

- Therapy is delivered at home via a homecare service. Attendance at hospital for blood transfusions and the management of complications of the disease are significantly reduced, allowing patients and carers to return to work and to a more active family life. PACE participants highlighted the avoidance of a number of intangible NHS and wider societal costs.

- Increased risk of infection requires vaccination against meningitis and the use of regular prophylactic antibiotics.

- Clinicians noted that there is an equity issue in routine access to this treatment across the UK.

- The PACE group felt strongly that this extremely clinically effective, well tolerated and life-saving therapy should be routinely available to eligible patients in NHS Scotland, via guidance from the NHSS specialist PNH Outreach Clinic

Summary of ultra-orphan decision-making framework

Eculizumab has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines. Relevant factors under each of the criteria are summarised below:

Nature of the condition
PNH is an extremely rare, progressively debilitating, and life-threatening genetic haematopoietic stem cell disease with high morbidity and mortality. Patients experience symptoms of extreme fatigue, difficulty swallowing, abdominal pain, and erectile dysfunction in males, all of which can be severe and limit the ability to function on a daily basis. End organ damage can occur leading to thrombosis, pulmonary hypertension and renal dysfunction. Median survival with conventional therapy is 10-15 years from diagnosis. Conventional management of PNH involves regular blood transfusions and use of anticoagulants.

At the PACE meeting, attention was drawn to the ongoing nature of the disease which can also be a large mental burden for the patient and their family.

Impact of the new technology
The TRIUMPH study showed that eculizumab significantly reduced the rate of haemolysis and improved anaemia compared with placebo in patients with transfusion-dependent PNH. Observational data from a subset of the PNH registry indicates that these benefits may also be achieved in patients with no history of transfusions. Uncontrolled data suggests that eculizumab reduces the incidence of thrombosis in patients with PNH. Studies have shown significant improvements on patient fatigue and health related quality of life scores.

At the PACE meeting it was noted that the positive impact of eculizumab on patient symptoms and quality of life is rapid and dramatic and allows patients to return to a normal life. Attention was also drawn to data showing that eculizumab is able to improve survival to a level comparable with the general population[9]. The economic analysis predicted a mean survival gain of 9.23 years.

Value for money
The company submitted a cost-consequence analysis comparing eculizumab with best supportive care (BSC) for the treatment of adults with PNH. In the economic evaluation, BSC was limited to blood transfusions; other therapies described as required, but not costed, include corticosteroids, anticoagulation and immunosuppressive therapies and medications for the treatment of chronic kidney disease, pulmonary hypertension, gastrointestinal damage and pain. SMC clinical experts have confirmed that BSC is the appropriate comparator.

A quality-adjusted life-year (QALY) based cost-consequence analysis was conducted using a Markov model structure. Although the analysis is described as a cost-consequence analysis, it is very similar to a cost-utility analysis but stops short of combining the incremental costs and QALYs gained to produce an incremental cost-effectiveness ratio. Patients entered the model in one of two states: 'PNH & no thrombosis' (68%) or 'PNH with previous thrombosis' (32%). Patients could transition to health states of PNH and initial thrombosis; PNH and subsequent thrombosis; PNH and end stage renal failure (ESRF); PNH, thrombosis and ESRF; and death.

Progression through the states in the model was based on data from the eculizumab clinical studies of patients and observation studies. Only eculizumab studies including patients with at least one transfusion in the prior 24 months were used. The model does not include other complications of PNH, such as pulmonary hypertension, gastrointestinal and other pain, and fatigue. The omissions were explained to be due to a lack of data on transitional probabilities and costs. A lifetime horizon was used and the company justified this on the basis that PNH is a chronic condition which requires a lifetime horizon to capture costs and benefits of treatment. Patients were said to be aged 39 at the start of the model and the time horizon was just under 100 years.

Eculizumab was assumed to reduce the thrombosis incidence rate from 11.13 events per 100 patient-years to 2.14 events per 100 patient-years, a relative reduction of 82% ($p<0.0005$). Once a patient treated with BSC had a thrombosis, it was assumed there was a 5.1 times greater risk of a subsequent thrombotic event compared to patients with no thrombosis. The distribution of severity of thrombosis used baseline data from the TRIUMPH study, with the same distribution applied to BSC and eculizumab treated patients.

The annual rates of ESRF in patients treated with eculizumab or BSC also came from clinical studies. Rates were low, being 0.005 for eculizumab-treated patients and 0.022 for BSC-treated patients. ESRF was assumed to improve for 25% of patients treated with eculizumab based on the TRIUMPH study; the remainder and those treated with BSC could only transition to also having a thrombosis or death.

Mortality rates were estimated as a function of background age-adjusted mortality, thrombosis- and ESRF-related excess mortality, and remaining PNH excess mortality. Scottish life tables informed background data mortality. Thrombosis- and ESRF-related excess mortality came from studies of non-PNH populations so may not reflect the mortality rate of PNH populations with these conditions. The same mortality rates were applied to BSC and eculizumab-treated patients. Mortality rates for BSC were adjusted using a 'PNH excess mortality' factor to give a predicted lifespan of 12.5 years, on the basis that 3 studies have reported estimated survival of between 10 and 15 years. A sensitivity analysis assumed a survival of 17.2 years with no adjustment.

Utility values were calculated using quality of life data collected at week 26 using the EORTC QLQ-C30 instrument in the TRIUMPH study. These were transformed into EQ-5D scores using a published regression model. The resulting values were 0.889 for patients without thrombosis or ESRF who were treated with eculizumab and 0.656 for similar patients treated only with BSC, a difference of 0.233. Utility decrements were applied for each different thrombotic event and were multiplied by the likelihood of each event to determine a weighted average decrement of 0.289. A similar level of decrement was applied to those with ESRF.

The analysis included drug acquisition and administration costs of eculizumab. For administration costs, the company assumed 80% of patients would be enrolled in the company-funded homecare programme which covers the cost of administration. The administration cost for 80% of patients was therefore excluded. For the remaining 20%, it was assumed that 26 annual administrations were required. The company confirmed that it is its intention to continue to fund the homecare programme. An additional cost for a meningococcal vaccine was also included, as specified in the SPC. No additional monitoring costs were included for eculizumab-treated patients.

No costs were included to account for adverse events. BSC treated patients were assumed to require 4.6 units of red blood cells annually, falling to 0.08 for those treated with eculizumab. Costs for thrombosis and ESRF were derived in the main from Scottish tariffs.

The company has provided a table comparing events avoided over time across the two arms for a cohort of 100 patients.

Table 1 Events avoided at 10, 20 and 40 years for a cohort of 100 patients.

Patients (of cohort of 100) experiencing:	Time from baseline		
	10 years	20 years	40 years
1 or more thrombolytic events			
BSC	61	73	76
Eculizumab	7	10	13
Avoided events	53	63	63
ESRF			
BSC	12	16	18
Eculizumab	5	9	16
Avoided events	7	7	2
PNH-related death			
BSC	39	71	90
Eculizumab	6	12	24
Avoided events	33	59	67

The company estimated an incremental quality-adjusted life-year (QALY) gain of 11.96, and a life year gain of 9.23. SMC would also wish to present the lifetime incremental cost of eculizumab but owing to commercial in confidence concerns raised by the submitting company, SMC is unable to publish this information. Please note that the annual medicine cost per patient per year is presented in the cost table below.

The results were sensitive to the assumed rate of excess deaths associated with PNH. When this was set to 0, the QALY gain reduced to 6.6. With no difference in utilities, the QALY gain reduced to 9.5. With a 20 year time horizon, the incremental QALY gain was 7.10. Results were not sensitive to the assumed level or costs of thrombosis and ESRF.

In addition to the high incremental costs relative to the QALY gains, the following limitations were noted:

- The additional mortality associated with PNH, which is assumed to reduce life expectancy to 12.5 years, is associated with some uncertainty, and was a key driver of the predicted benefits.
- The clinical events data used in the BSC arm did not come from the long-term extension study but were informed by observational studies and a hazard rate applied from the extension study. A comparison of the modelled data with data from the extension study at 5.5 years showed the model over-predicted death and thromboembolism events. In the extension study, 96.4% of patients were event-free compared to 90.4% as modelled, and 2.4% had died compared to 3.1% as modelled.
- The utility values for patients treated with eculizumab imply such patients have a higher quality of life than the general population; however, setting the value at that of the general population only reduced the QALY gain by a small amount to 11.41. In general, the results were more sensitive to changes in life expectancy than quality of life.

- Not all patients covered by the indication are represented in the clinical studies that have informed the parameters used in the model; excluded groups are those not receiving transfusions and children.
- The only BSC resource and cost which reduced with eculizumab treatment was blood transfusions. No benefit was assumed from fewer complications related to pulmonary hypertension, pain and gastrointestinal problems. These are conservative assumptions. Further conservative assumptions related to the model not capturing other possible treatment impacts eg on pulmonary hypertension or gastrointestinal damage.

Patient and clinician engagement
A Patient and Clinician Engagement (PACE) meeting was held for this submission. Participants at the PACE meeting indicated a range of potential impacts of the new technology for the patient and families/carers

Impact beyond direct health benefits and on specialist services
At the PACE meeting, attention was drawn to the dramatic psychological benefit of eculizumab on patients, families and carers as a result of the substantial reduction in risk of thrombosis.

The company estimated wider societal costs based on feedback from PNH Scotland, a UK PNH patient survey and information from the available literature. This included annual indirect costs attributable to PNH of up to £4,700 per patient to government (e.g. from disability payments), £400 to patient and carer (e.g. travel costs and home adaptations) and £15,000 to society (loss of productivity).

At the PACE meeting, it was noted that the median age of presentation of PNH was 30-40 years. Among PNH patients of working age in Scotland, approximately half had to stop work because of PNH. Subsequent treatment with eculizumab has allowed some of these patients (and carers) to return to work.

No additional infrastructure will be required in the NHSS specialist PNH Outreach Clinic.

Costs to NHS and Personal Social Services
SMC would wish to present the estimated budget impact of eculizumab for NHS Scotland, but owing to commercial in confidence concerns raised by the submitting company SMC is unable to publish this information.

The Committee also considered the benefits of eculizumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the following criteria were satisfied: a substantial improvement in quality of life; and the absence of other treatments of proven benefit. In addition, as eculizumab is an ultra-orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee was unable to accept eculizumab for use in NHS Scotland.

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

Summary of patient and public involvement

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

- A submission was received 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. This can range from simply being unable to do normal daily tasks to being carried up and down stairs, needing to be dressed by someone else or being too tired to wash. For many, the exhaustion is extremely debilitating leaving them unable to look after their own children, go to work or have a relationship.
- Patients currently require regular blood transfusions to keep their haemoglobin levels up. These can be 4-6 hours in length and often do not get rid of the fatigue or other PNH symptoms. Patients are also treated with the anti-coagulant, warfarin. However, it does not eliminate the risk of life-threatening thromboses, does not reduce symptoms such as tiredness and patients can struggle to keep their INR stable.
- Eculizumab may give patients back a normal life expectancy, reduce the risk of a fatal clot and has been shown to improve symptoms such as fatigue in patients. This may allow them to return to work and to a normal family life, meaning they no longer feel a burden to those they love the most.

Additional information: guidelines and protocols

According to experts consulted, treatment of PNH in Scotland is largely guided by the English National PNH Service, commissioned by NHS England.[11] Guidance for this service is documented in its Standard Contract, which states that eculizumab is indicated for PNH patients (adults and adolescents) with any of the following characteristics:

- transfusion dependent (four or more transfusions in 12 months)
- 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.[11]

The 2015 British Committee for Standards in Haematology (BCSH) 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]

Additional information: comparators

Eculizumab is the first medicine specifically aimed at treating PNH. The relevant comparator is supportive care, comprising blood transfusions for anaemia and thromboprophylaxis with warfarin or heparin. The only curative therapy is bone marrow transplant in suitable patients for whom a donor can be found.

Cost of relevant comparators

Drug	Dose Regimen	Cost Per Year (£)
Eculizumab	**600mg by IV infusion once a week for the first four weeks followed by 900mg by IV infusion in the fifth week then 900mg by IV infusion every 14 (±2) days***	**252,000 in the first year and 245,700 in subsequent years**

Costs from MIMS on 26 November 2015. *Adult dosing schedule, dosing in paediatric patients differs. The lowest dose in paediatric patients costs £56,700 per year.

Additional information: budget impact

SMC is unable to present the estimated budget impact of eculizumab for NHS Scotland as the submitting company has indicated that this information is commercial in confidence.

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

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. The European Medicines Agency (EMA) European Extension of indication variation assessment report Soliris 26 February 2015 Committee for Medicinal Products for Human Use (CHMP) Procedure No. EMEA/H/C/000791/II/0066 26 February 2015 www.ema.europa.eu

2. Hillmen P, Young NS, Schubert J et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2006;355(12):1233–43.

3. Brodsky RA, Young NS, Antonioli E et al. Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. Blood. 2008 111(4):1840–7.

4. Hillmen P, Elebute M, Kelly R et al. Long-term effect of the complement inhibitor eculizumab on kidney function in patients with paroxysmal nocturnal hemoglobinuria. Blood. 2007 110:4123–8.

5. Hillmen P, Muus P, Röth A et al. Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria. Br J Haematol. 2013 162(1):62–73.

6. Eculizumab 300mg concentrate for solution for infusion (Soliris®) Summary of product characteristics. Alexion Pharma UK Ltd. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 30 September 2015

7. The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) Assessment report Soliris Procedure No. EMEA/H/C/000791/II/0050 21 March 2013 www.ema.europa.eu

8. The European Medicines Agency (EMA) European Public Assessment Report. Scientific discussion Eculizumab 300mg concentrate for solution for infusion (Soliris®) 29/06/2007 www.ema.europa.eu

9. Kelly RJ, Hill A, Arnold LM et al, Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival. Blood. 2011 117 (25): 6786-92

10. Martí-Carvajal AJ, Anand V, Cardona AF, Solà I. Eculizumab for treating patients with paroxysmal nocturnal hemoglobinuria. Cochrane database Syst Rev. 2014 Jan;10(10):CD010340

11. PNH National Service http://www.pnhleeds.co.uk/professionals/indication-for-treatment-with-eculizumab/.

12. Killick SB, Bown N, Cavenagh J et al. on behalf of the British Society for Standards in Haematology. Guidelines for the Diagnosis and Management of Adult Aplastic Anaemia; 2015.

This assessment is based on data submitted by the applicant company up to and including 11 January, 2016.

*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_statements/Policy_Statements

Drug 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.

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.