

# Caplacizumab with plasma exchange and immunosuppression for treating acute acquired thrombotic thrombocytopenic purpura

Technology appraisal guidance

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## Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

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# 1 Recommendations

- 1.1 Caplacizumab with plasma exchange and immunosuppression is recommended, within its marketing authorisation, as an option for treating an acute episode of acquired thrombotic thrombocytopenic purpura (TTP) in adults, and in young people aged 12 years and over who weigh at least 40 kg. Treatment should be started and supervised by physicians experienced in managing thrombotic microangiopathies. It is recommended only if the company provides caplacizumab according to the [commercial arrangement](#).

## Why the committee made these recommendations

Standard care for an acute episode of acquired TTP includes plasma exchange and immunosuppressant medicines. Trial results show that, compared with standard care alone, caplacizumab plus standard care reduces:

- the time it takes to bring platelet levels back to normal
- the number of plasma exchange treatments needed
- time in hospital and intensive care.

Adding caplacizumab likely reduces the long-term complications of acquired TTP and risk of death around the time of an acute episode, but it is unclear by how much. This is because the trial results do not address whether adding caplacizumab improves either length or quality of life in the long term after people stop taking the drug. Also, there are limited reported data on the long-term complications of acquired TTP after an acute episode.

However, the assumptions in the economic modelling are plausible. Also, there are potential benefits with caplacizumab that are not included in the cost-effectiveness estimates. Overall, the estimates are within the range normally considered a cost-effective use of NHS resources. So, caplacizumab is recommended for treating acute acquired TTP.

## 2 Information about caplacizumab

### Marketing authorisation indication

- 2.1 Caplacizumab (Cabliivi, Sanofi) has a marketing authorisation for treating adults and young people aged 12 years and over who weigh at least 40 kg who are 'experiencing an episode of acquired thrombotic thrombocytopenic purpura, in conjunction with plasma exchange and immunosuppression'.

### Dosage in the marketing authorisation

- 2.2 The dosage schedule is available in the [summary of product characteristics](#).

### Price

- 2.3 The list price of caplacizumab is £4,143 per 10-mg vial (excluding VAT; BNF online, May 2020). The company has a [commercial arrangement](#). This makes caplacizumab available to the NHS with a discount. The size of the discount is commercial in confidence.

## 3 Committee discussion

The appraisal committee ([section 5](#)) considered evidence submitted by Sanofi, a review of this submission by the evidence review group (ERG), the technical report, and responses from stakeholders. See the [committee papers](#) for full details of the evidence.

### Current treatments and patient perspectives

#### **Acquired thrombotic thrombocytopenic purpura is a life-threatening condition associated with long-term morbidity and mortality**

- 3.1 Acquired thrombotic thrombocytopenic purpura (TTP) is a rare autoimmune condition characterised by antibodies against ADAMTS13, the enzyme that cleaves von Willebrand factor, a large protein involved in blood clotting. People with low levels of ADAMTS13 activity have a higher risk of clotting. The condition causes blood clots in small blood vessels, which leads to decreased blood flow and oxygen supply to vital organs such as the brain, heart and kidneys. This causes ischaemic damage, can be acutely life-threatening, and, in the longer term, may cause cognitive deficits, depression and hypertension. One clinical expert stated that acquired TTP is the most dangerous acute illness in haematology, with some people transitioning from having no symptoms to death within hours. There are treatments for acquired TTP (see [section 3.2](#)), and it can relapse. The patient experts explained that acquired TTP can affect quality of life and, in particular, mental health. The committee was told that people with newly diagnosed acquired TTP are likely to be anxious, which is made worse by them never having heard of the condition. Even when acquired TTP is in 'remission', the condition can relapse. Also, the signs and symptoms of relapse may be non-specific. One patient expert suggested that anxiety itself is a symptom of an upcoming relapse and can lead to long-term depression. The committee concluded that acquired TTP is a life-threatening, stressful condition associated with long-term morbidity and mortality.

## **Caplacizumab is added on to, but does not replace, existing treatment with plasma exchange and immunosuppressants**

3.2 After diagnosis of an acute episode of acquired TTP, current standard treatment involves plasma exchange, ideally within 4 to 8 hours of diagnosis. This involves filtering blood to remove the antibody-containing plasma and replacing discarded plasma with donated plasma to replace ADAMTS13. Immunosuppressant drugs such as corticosteroids and rituximab treat the underlying autoimmune condition, and limit antibody production against ADAMTS13. Caplacizumab binds to von Willebrand factor, inhibiting it from interacting with platelets, and preventing clots. The first dose is given intravenously at the first plasma exchange. The subsequent doses are given subcutaneously daily for up to 30 days after stopping plasma exchange or longer, if necessary, until ADAMTS13 levels normalise. The clinical experts stated that controlling the underlying immune condition can take up to 10 days with rituximab treatment, and that caplacizumab treatment reduces blood clot formation during this time. The clinical experts explained that the longer the blood vessels remained blocked, the higher the risk of illness and dying. They further stated that, because of the risk of relapse, clinicians continue to monitor people with acquired TTP in remission and to offer rituximab to reduce relapse risk. The committee concluded that caplacizumab does not replace existing treatment, but is added to plasma exchange to increase platelet counts and reduce blood clots.

## **Plasma exchange is unpleasant, and people with acquired TTP would welcome a treatment that reduces plasma exchange and hospital stays**

3.3 Although caplacizumab does not replace plasma exchange, it may reduce the number of days of plasma exchange and the volume of plasma needed (see [section 3.7](#)). Plasma exchange involves inserting an intravenous catheter, which carries a risk of infection. The clinical experts stated that the catheters are typically replaced every 5 to 7 days. This means that treatments that reduce the number of days of plasma exchange would also reduce the need to replace catheters. The patient experts described how inserting catheters is uncomfortable, painful and stressful, in part, because of infection risk. They stated that, of all the

reported benefits of caplacizumab, they most welcome reducing plasma exchange, and time in intensive care. One patient expert who had used caplacizumab stated that people might struggle with injecting caplacizumab at home or with its adverse effects, such as nosebleeds. However, they thought that people would be willing to accept these if treatment reduced hospital stays and the need for plasma exchange. The committee concluded that plasma exchange and hospital stays are unpleasant, and that people with acquired TTP would welcome a treatment that reduces these.

## **A new NHS specialised service for acquired TTP is being established**

3.4 The clinical experts stated that the UK has had fragmented care for people with acquired TTP. This has led to poorer outcomes, including higher death rates outside of specialist centres for acquired TTP. For example, estimates of death rates were 10% to 20% in non-specialist centres and less than 5% in specialist centres. People are currently referred to specialist centres for acquired TTP treatment. However, diagnosis and treatment may be delayed because many clinicians are unaware of acquired TTP, and because of the distance someone has to travel to access a specialist centre. The commissioning lead of the NHS Highly Specialised Services stated that, if recommended, the NHS would commission caplacizumab through a new specialised service. The NHS aims to have up to 9 specialist centres in England, providing clinical expertise and geographical access for patients. If caplacizumab were to be recommended, some people could have it locally, supervised remotely by a specialised centre. A clinical expert said that kits are now available for emergency departments to diagnose acquired TTP within 24 hours. The committee acknowledged that there is regional variation in the time to diagnosis of acquired TTP, in treatment and in patient outcomes. It concluded that a new NHS specialised service will attempt to reduce this variation and improve outcomes.

## **Clinical trial results**

### **The main clinical trial, HERCULES, is broadly generalisable to UK**



## clinical practice

3.5 There were 2 placebo-controlled trials of similar design in the clinical trial programme for caplacizumab: HERCULES and TITAN. Both were double-blind randomised controlled trials. TITAN included 75 people and HERCULES included 145 people having an acute episode of acquired TTP. Both compared caplacizumab plus standard care (plasma exchange, immunosuppressant medication including rituximab; from now referred to as caplacizumab) with placebo plus standard care (from now referred to as standard care alone). Because of protocol amendments and violations, TITAN was not used to support the company's application for a marketing authorisation for caplacizumab and was not presented to the committee for its first meeting. Caplacizumab's marketing authorisation states that it should be given before people start plasma exchange. However, in HERCULES, caplacizumab was started after plasma exchange. This was because the time needed to consent and randomise patients could delay plasma exchange, which was neither practical nor safe. One clinical expert stated that, in clinical practice, caplacizumab would be given before and within the same day as plasma exchange. Also, the trial recruited people in specialist centres for acquired TTP rather than from general haematology centres; the clinical experts considered that people in the trial may have had better outcomes than would be seen in overall NHS practice. However, this was unlikely to have affected caplacizumab's relative treatment effect. The trial included only 18 people from the UK, and 1 clinical expert said that:

- the people in the trial, and the treatments they had, reflected UK practice
- since 2018, some patients under her care have had caplacizumab via a global compassionate use scheme
- the trial outcomes in the caplacizumab arm reflected the outcomes she had seen in NHS practice when using caplacizumab through the compassionate use scheme.

The committee concluded that results of HERCULES were generalisable to the centres in which caplacizumab would be offered in UK clinical practice.

## The outcomes in HERCULES are clinically relevant, but do not

## include the short- and long-term complications in the economic model

3.6 HERCULES measured clinical outcomes around an acute episode of acquired TTP. Data were collected while people were on treatment for up to 30 days, and for 28 days after they stopped treatment. The committee understood that an observational single-arm extension to HERCULES is ongoing. The primary outcome of the trial was time to platelet normalisation. The clinical experts explained that they considered platelet count to be a surrogate measure for more meaningful outcomes reflecting morbidity and mortality. From a clinical expert, the committee heard that the faster the platelet count is normalised, the lower the risk of complications. Key secondary outcomes in the trial analyses in the company's statistical analysis plan, listed hierarchically, were:

- a composite outcome of TTP-related death, disease recurrence while on treatment and major thromboembolic event
- disease recurrence alone including the 4-week follow up
- the proportion of people whose condition did not respond to treatment ('refractory' TTP)
- time to normalisation of all 3 blood markers of organ damage: lactate dehydrogenase, cardiac troponin and creatinine.

Other secondary outcomes such as volume and duration of plasma exchange, time in hospital or intensive care, and death were not tested statistically in line with the company's statistical analysis plan. The clinical experts explained that all the measured outcomes were clinically relevant. The patient experts said that plasma exchange use and time in hospital are important (see [section 3.3](#)). The committee concluded that the primary surrogate and the secondary outcomes in HERCULES were clinically relevant. However, it noted that the trial did not measure the effects of caplacizumab in the company's health-economic model (see [sections 3.13 to 3.18](#)) on survival, quality of life, disability or mental health in the long term.

## **HERCULES shows that caplacizumab reduces time to platelet normalisation, plasma exchange use and duration of hospital stay**

3.7 The committee reviewed the results of HERCULES, noting that:

- Caplacizumab reduced the time to the primary outcome, platelet normalisation. There was a very small (0.2 days) difference in median time to platelet normalisation between the treatments (2.7 days on caplacizumab and 2.9 days on placebo;  $p < 0.01$ ). The clinical experts explained that the rate of platelet normalisation was similar between the 2 trial arms until day 3, but then caplacizumab added benefit to plasma exchange in normalising platelet levels until the autoimmune condition was controlled.
- Caplacizumab reduced the secondary composite outcome (12% of people on caplacizumab compared with 49% on standard care alone had an acquired TTP-related death, disease recurrence while on treatment or a major thromboembolic event;  $p < 0.001$ ). The same proportion (8%) of people randomised to each treatment had a major thrombotic event (a component of the composite outcome) during the acute period.
- Caplacizumab reduced the proportion of people whose disease recurred while on treatment or in the 28 days after stopping treatment (13% on caplacizumab compared with 38% on standard care alone;  $p < 0.001$ ).
- Caplacizumab reduced the proportion of people whose acquired TTP was refractory to plasma exchange treatment (meaning that there was no improvement in platelet count after 5 plasma exchanges and treatment with corticosteroids). No people in the caplacizumab arm had acquired TTP refractory to plasma exchange. The company has said that the proportion whose acquired TTP was refractory in the standard care arm is academic in confidence and cannot be reported here.
- Caplacizumab reduced the mean duration of plasma exchange (6 days compared with 9 days on standard care alone), mean volume of plasma exchange (21 litres compared with 36 litres), and mean days in hospital (10 days compared with 14 days) and in intensive care (3 days compared with 10 days). The committee noted that, in the company's statistical plan, these outcomes were described, but not statistically tested. One clinical expert explained that she had seen a similar reduction in number of plasma exchanges and length of hospital stay with caplacizumab in the compassionate use

programme in her centre.

The committee concluded that caplacizumab is clinically effective in the acute period compared with standard of care alone.

## **It is not possible to estimate reliably how much caplacizumab might reduce deaths in the acute period from trial data**

3.8 The HERCULES trial did not aim to assess whether caplacizumab reduced deaths around an acute episode. The company explained that to do this, it would have needed to recruit more people, which would have been difficult because acquired TTP is rare. Instead, the company used observational data to quantify its claims of caplacizumab's effect on mortality during an acute episode (see [section 3.11](#)). The committee noted there were few deaths in the caplacizumab and standard care arms in the trial (including during follow up when people had stopped treatment):

- In the first meeting, the company presented data on mortality from HERCULES only: 1 death occurred in the caplacizumab arm (1%) and 3 deaths occurred in the standard care arm (4%). The ERG estimated a risk ratio for death of 0.34 (95% confidence interval [CI] 0.04 to 3.22) for caplacizumab compared with standard care only.
- In the second meeting, the company presented pooled data from HERCULES and TITAN: 1 death occurred in the caplacizumab arm (1%) and 5 deaths occurred in the standard care arm (4%). The ERG estimated a risk ratio for death of 0.21 (95% CI 0.03 to 1.75) for caplacizumab compared with standard care only.

The committee considered that there were too few deaths, even when pooling data from the 2 trials, to estimate accurately the effect of caplacizumab on survival in the acute period. It was aware that the company had chosen not to use the trial data on deaths in its original cost-effectiveness model (see [section 3.11](#)), but instead used data from a global compassionate use scheme. The committee noted that the considerable uncertainty reflected in the wide confidence intervals also included the possibility that caplacizumab increased the risk of dying. It concluded that it was not possible to estimate reliably the

extent of the benefit using the randomised trial data.

## The company's economic model

### The company's model structure is appropriate for decision making

3.9 The company's model had 2 parts: 1 for acute illness and 1 for the rest of a person's life. It also included the possibility of relapse, that is, a person who recovers cycles through the model again. The committee appreciated that people only have treatment with caplacizumab during an acute episode, and that people do not have caplacizumab to prevent relapses. The company modelled events around an acute episode of acquired TTP using a decision-tree model. It used a Markov model to project long-term events for up to 55 years after a person had recovered from an acute episode. The committee understood that the company considered that with caplacizumab, compared with standard care:

- In the acute period (decision-tree model):
  - Treatment decreases the risk of dying (see [section 3.11](#) and [section 3.12](#)) from an estimated baseline risk of dying on standard care (see [section 3.10](#)).
  - Treatment improves quality of life because people need fewer plasma exchanges. The extent of this improvement is based on an assumption (see [section 3.18](#)).
- In the long term (Markov model):
  - Former treatment with caplacizumab decreases the risk of dying (see [section 3.15](#) and [section 3.16](#)) from an estimated baseline risk of dying for people with acquired TTP who had standard care for their acute episode (see [section 3.13](#)).
  - Treatment improves quality of life by decreasing the rate of long-term complications. The modelled complications included cognitive impairment and mental health problems such as depression and anxiety. The company estimated the rates of long-term complications after standard care for the

acute episode (see [section 3.14](#)).

Because there were no long-term data, the company estimated the extent to which caplacizumab reduced the rate of long-term complications by assuming that the treatment effect of caplacizumab for acute outcomes would be the same as its treatment effect for long-term outcomes (see [section 3.15](#) and [section 3.16](#)). The company modelled the same rates of relapse on caplacizumab and on standard care alone (see [section 3.17](#)). The acute-period model included the costs of treatment and of hospital stay. The long-term model included the costs of treating a relapse and complications of acquired TTP, and of preventative rituximab. The committee noted that many of the treatment effects ascribed to caplacizumab in the model were based on either assumptions or non-trial data, which increased uncertainty (see [sections 3.10 to 3.18](#)). However, the committee considered that the economic model captured relevant aspects of acquired TTP, and concluded that its overall structure was appropriate for decision making.

## **The submodel reflecting acute disease takes into account that mortality rates on standard care have improved over time**

3.10 The company and the clinical experts stated that the number of deaths in the trial in both arms were lower than would be expected in clinical practice. Because of this, the company did not use death rates from HERCULES to estimate absolute death rates for standard care in its model. Instead:

- In its original submission for the committee's first meeting, the company meta-analysed 129 international studies that had reported deaths around an acute episode of acquired TTP in people who had standard care including plasma exchange. It extracted the probability of dying during an acute episode. This analysis suggested an average probability of dying of 13.2% during an acute hospitalisation. The committee noted that the meta-analysis included studies with very heterogeneous results (the probability of dying ranged from 0% to 57%). The committee noted that the company's meta-analysis had not been adjusted for risk of death at baseline. The committee considered that restricting the analysis to 7 UK studies was more generalisable to the UK. It considered that the most relevant UK studies resulted in a probability of dying

during an acute episode of around 7.0%.

- In its response to the appraisal consultation document for the committee's second meeting, the company provided a new estimate for deaths on standard care during the acute period of 12.6%, based on a poster presentation (Lester et al. 2015) that reported Hospital Episode Statistics for new cases of acquired TTP and Office of National Statistics data for deaths from acquired TTP between 2003 and 2013.

The committee considered that the new estimate for standard care (12.6%) was more generalisable than the estimate from the meta-analysis because it included patients in England only. However, it agreed that it may overestimate the true risk of dying because standard care may have improved since the period during which the data were collected. After the second meeting, the committee concluded that it was likely that the probability of dying during an acute episode on standard care is between 7.0% and 12.6%. For the third and fourth meetings, the company used in the modelling a value of 10%, which the committee accepted.

## **The benefit of caplacizumab on mortality in the acute period based on comparing separate sources of observational data may be biased**

3.11 In its original base case, the company did a naive (unadjusted) comparison of observational data from separate sources to estimate the comparative benefit of caplacizumab compared with standard care on the risk of dying during an acute episode:

- For caplacizumab, the company used data from a global compassionate use scheme in which the company provided clinicians with caplacizumab on request (239 people had had treatment up to February 2020). These data suggested an absolute probability of dying on caplacizumab of 3.8% (9 deaths) over a period equivalent to the follow up in HERCULES (the acute episode plus about 3 months).
- For standard care, the company used a probability of dying around an acute episode of 13.2% from its meta-analysis (see [section 3.10](#)).
- Naively comparing the data from these separate populations gave an estimated

relative risk for survival with caplacizumab of 0.29 compared with standard care alone. This suggested that caplacizumab reduced the chance of death in the acute period by 71% compared with standard care alone.

The committee heard that, in the compassionate use scheme, caplacizumab was given in centres of excellence, and the clinical experts explained that patient outcomes, including the death rate, were better in these centres compared with non-specialist centres (see [section 3.4](#)). It agreed that, because caplacizumab would likely be commissioned for use only in these centres, the absolute rate of death for people having treatment with caplacizumab was likely to be valid. However, the committee considered that any relative risk comparing treatment with and without caplacizumab would overestimate the effectiveness of caplacizumab because treatment in specialist centres improve outcomes and that the relative benefit ascribed to caplacizumab was very likely to be confounded. The committee concluded that this bias likely overestimated the clinical and cost effectiveness of caplacizumab.

## **The company's estimates of the benefit of caplacizumab on mortality based on trial data are not robust and are overestimated**

3.12 In response to the appraisal consultation document, the company provided alternative estimates of the benefit of caplacizumab in reducing deaths during an acute episode. In its base case for the second and subsequent appraisal committee meetings, it used a risk ratio of deaths during an acute episode with caplacizumab compared with standard care alone from the clinical trials of caplacizumab (see [section 3.8](#)). These risk ratios were 0.21 using pooled HERCULES and TITAN data, and 0.34 using HERCULES data alone. The committee was concerned that the risk ratios calculated from the caplacizumab trials were not robust because they were based on few events. The committee considered that the magnitude of reduction in deaths seemed high compared with the treatment effect of thrombolytic treatments used for other conditions with life-threatening blood clots. It considered that, given the high levels of uncertainty, and taking into account its consideration on other estimates (see [section 3.11](#)), a more conservative assumption should be used. The committee, at its second meeting, suggested a relative risk



of 0.5. This represented a 50% reduction in acute deaths with caplacizumab as a reasonable modelling assumption, given the uncertainty around the company's estimates. The company chose to continue to model the relative risk of 0.34 in its base case when presenting for the committee's third and fourth meetings. The committee concluded that relative risk reduction of 0.5 reflected a reasonable reduction in mortality given the lack of robust evidence.

## **In the long-term submodel, the company's revised calculation of a standardised mortality ratio to estimate death rates is appropriate**

3.13 To determine the absolute risk of death after an acute episode over the long term in people who had had standard care alone, the company calculated a standardised mortality ratio and applied it to the risk of dying in the UK general population. The standardised mortality ratio reflects observed deaths after standard care during an acute episode divided by the expected number of deaths for the general population of similar age and sex. The company used Upreti et al. (2019), which describes mortality over a median 3-year follow up in people who survived an acute episode of acquired TTP and who were followed at John Hopkins Hospital, Baltimore, US, between 1995 and 2018. The company calculated the standardised mortality ratio as 8.3 (meaning that a person with acquired TTP is about 8 times more likely to die than a person of the same age and sex without acquired TTP). The company explained that it calculated the ratio using the UK population. The committee appreciated that about 60% of the Upreti cohort comprised people of African-American family origin, and that 14% of deaths were caused by HIV, which likely did not reflect the characteristics of the UK general population. The committee considered that this likely overestimated the standardised mortality ratio. After the second meeting, the company revised its calculations of the standard mortality ratio so that the estimates of mortality reflected the US general population mortality, resulting in a lower standardised mortality ratio of 5.1. In response to consultation, the company provided additional validation of its mortality assumptions and concurred with the committee that there was a paucity of long-term mortality data in this disease area. The committee concluded that the company's revised calculation of a

standardised mortality ratio to estimate death rates used an appropriate reference population.

## **In the long-term submodel, the rates of complications on standard care modelled by the company may not be generalisable to the UK**

3.14 After recovering from a first episode of acquired TTP, some people will have long-term complications from ischaemic damage (see [section 3.1](#)). The company assumed that treatment with caplacizumab lowers the risk of these complications. In its Markov model, it modelled the prevalence of cognitive impairment and mental health problems (such as depression and anxiety) in people with acquired TTP having standard care alone over the lifetime of the modelled populations. The committee considered that the company's estimates of the prevalence of long-term complications in people with acquired TTP:

- did not come from a UK population
- included people whose complications were not specifically associated with acquired TTP
- reflected estimates of severe depression in people in a TTP support group in the US rather than a random sample of people with acquired TTP in the UK.

The committee appreciated the company's attempts to ensure that it had exhausted possible sources of data. It concluded that the company had not shown that the prevalence of long-term complications on standard care in its model were generalisable to current UK practice. However, it further concluded that, in the absence of any other data, it was reasonable to use the company's estimates in the model.

## **The relationship between length of hospital stay and long-term complications and death is unclear**

3.15 Because HERCULES measured outcomes during an acute episode only, it did not provide data for caplacizumab compared with standard care on long-term complications when acquired TTP is in remission. However, the

company assumed that previous treatment with caplacizumab reduced complications and extended life in the remission period above and beyond a benefit to mortality in the short term. After estimating a risk of death for people on standard care (see [section 3.13](#)), the company assumed that time in intensive care or hospital was causally related to the prevalence of long-term outcomes including cognitive impairment and mental health (including depression, anxiety, post-traumatic stress), and the relative risk of death for caplacizumab compared with standard care in the Markov submodel. It assumed that this equalled the ratio (0.62) of time in intensive care and hospital measured in HERCULES for caplacizumab compared with standard care alone. The committee noted that caplacizumab was not disease modifying and would not be expected to work after people stopped having it. However, the committee understood that reducing thromboses and the likelihood of complications in the short term would reduce the risk of sequelae from these complications in the longer term. The clinical experts stated that a relationship between hospital stay and long-term outcomes was plausible. The committee noted that a relationship between length of stay and the development of subsequent complications in the longer term had not been validated, and that the company had not presented relevant data. The committee recalled that the same proportion of people in each arm of HERCULES developed a major thromboembolic complication during the trial. The company responded that it did not consider that major thromboembolic events would capture differences in microvascular damage between caplacizumab and standard care. The committee was also aware that some people might have pre-existing complications that might prolong stay in hospital and that caplacizumab would not improve or cure. In response to consultation after the committee's first meeting, the company confirmed that there were no data specific to acquired TTP to validate a causal relationship between length of hospital stay and long-term outcomes. The committee concluded that it was not possible to validate a causal link between former treatment with caplacizumab and long-term complications and death beyond the end of the trial based on length of hospital stay.

## Time to platelet normalisation is better than hospital stay for estimating long-term outcomes, but uncertainty remains

3.16 In response to consultation after the committee's first meeting, the company presented 2 exploratory analyses. These used time to platelet normalisation rather than duration of hospitalisation as an alternative proxy for long-term outcomes. They were:

- an analysis based on a randomised controlled trial comparing plasma exchange and another treatment, plasma infusion (Rock et al. 1991), which showed an association between having a shorter time to platelet normalisation and a lower death rate at 6 months
- an analysis based on a retrospective cohort study (Liu et al. 2013), which showed that platelet normalisation by 3 days after starting treatment compared with platelet normalisation after 3 days was associated with fewer deaths over 80 months.

The committee considered that:

- time to platelet normalisation better approximated a person's exposure to microthrombi than time in hospital during an acute episode, and the clinical experts explained that microthrombi increase the risk of long-term complications (see [section 3.15](#))
- it was plausible that a causal relationship between time to platelet normalisation in the acute period and long-term complications existed
- the exact relationship between time to platelet normalisation and long-term outcomes remained uncertain because:
  - Liu et al. and Rock et al. did not provide data on the prevalence of long-term complications, other than death, after an acute episode
  - in both of these studies, some of the deaths would have been during an acute episode rather than afterwards
  - the studies were several years old, particularly Rock et al., so it was questionable how generalisable they would still be to current NHS.

The company adjusted the risk ratio for time to platelet normalisation for

caplacizumab compared with standard care in HERCULES. This was to account for the possibility that not all of the benefit of caplacizumab in reducing the time to platelet normalisation would translate to a benefit in reduced long-term complications and deaths. The risk ratio for time to platelet normalisation in HERCULES (0.57) was multiplied by 1.16 (the 85% reduction in time to platelet normalisation in Rock et al. with plasma exchange compared with plasma infusion divided by the 75% reduction in deaths with plasma exchange compared with plasma infusion). The committee considered that the estimated size of benefit with caplacizumab on complications was plausible. However, it thought that there was uncertainty about whether this would translate to a benefit in survival after people had recovered from their acute TTP episode. So, the committee concluded that using an estimated risk ratio of 0.66 to estimate the effect of caplacizumab compared with standard care in reducing long-term cognitive impairment and mental health problems would be appropriate, although still highly uncertain. For the endpoint of death in the Markov submodel, the committee considered in its second committee meeting that a risk of 0.90 was plausible. However, it was willing to consider a value of 0.80 presented by the company to NICE in its third and fourth committee meetings (which represented a midpoint between the company's estimate of 0.66 and 0.90) in its decision making.

## **The company's modelled rate of relapse is appropriate, but it is not known whether caplacizumab works equally well if used again**

3.17 The committee appreciated that someone could have caplacizumab again after each relapse. The company assumed an annual disease relapse rate of 1%, based on the opinions of clinicians it surveyed. One clinical expert at the meeting noted that the increased use of rituximab to prevent relapse meant that the relapse rate in the UK was now lower than it had been before rituximab was standard care. However, he thought that 1% per year was too low, and that a more realistic estimate would be somewhere between 1% and 5%. The company assumed that caplacizumab works as well on retreatment as it does when first used, but did not present data to support this. The committee asked the company whether there was any evidence of antibodies against caplacizumab from the available trial data, and whether the effectiveness of caplacizumab would differ on retreatment. The company stated that it

had seen antibodies in some patients. The committee concluded that the relapse rate was likely to be higher than 1% in clinical practice. It was also uncertain about whether caplacizumab was as effective on reuse as with initial use.

## **Information on quality of life is not available from HERCULES, and caplacizumab's effect on quality of life remains uncertain**

3.18 There were no quality-of-life data collected in HERCULES. The company instead used quality-of-life data from people hospitalised with stroke to estimate quality of life during an acute episode of acquired TTP. This resulted in a baseline utility value of 0.64. The committee stated that this appeared to be high, suggesting better quality of life than would be expected for people in hospital for a life-threatening condition (see [section 3.1](#)). The patient experts said that this did not reflect how severely an acute episode affected people. In response to consultation after the committee's first meeting, the company revised this assumption so that the utility on standard care was half (0.32) that of caplacizumab (0.64). The committee considered that quality of life would be better around an acute episode with caplacizumab compared with standard care because of the fewer plasma exchanges needed. However, it thought that an assumption of a 25% reduction in quality of life on standard care rather than the company's assumption of a 50% reduction was appropriate. Having heard from the patient experts that acquired TTP affects mental health (see [section 3.1](#)), the committee also considered whether quality-of-life estimates for acquired TTP should have included an estimate of the fear of relapse. For the committee's second meeting, the company included an estimate of disutility for fear of relapse. However, the company included it only for patients having standard care, and not for people having caplacizumab. The committee agreed that it had not been proven that caplacizumab reduced relapse frequency, so was not convinced that any disutility would affect the standard care only arm. Furthermore, it agreed that it was likely that the model already included the disutility of a fear of relapse, via anxiety and depression reflected in the Markov submodel. The committee noted that the company had estimated the quality of life associated with cognitive impairment and mental health in the long term. This was based on studies in people with stroke and people with depressive disorder

respectively. It acknowledged that cognitive impairment and mental health problems would lower a person's quality of life. However, it recalled that there was no direct evidence that caplacizumab would decrease the likelihood of having these complications or improve quality of life by decreasing these complications (see [section 3.15](#) and [section 3.16](#)). The committee noted that the utility values did not have a large effect on incremental cost-effectiveness ratios (ICERs). It concluded that the effect of acquired TTP lowers quality of life, and that treatment with caplacizumab improves quality of life but by how much is uncertain.

## **Some potential cost savings associated with caplacizumab may not be included in the company's model**

3.19 The committee understood that using caplacizumab lowered the cost of plasma exchange and hospital stay compared with best supportive care. The model included cost of testing ADAMTS13 activity, as well as adverse events associated with treatment. The committee noted that the company modelling did not include the costs of escalating treatment for acquired TTP refractory to treatment. This would favour standard care because more people in the standard care arm in HERCULES were refractory to treatment than in the caplacizumab arm (see [section 3.7](#)). The company stated that, based on its observations from the compassionate use scheme for caplacizumab, in NHS clinical practice, people would have it for a shorter duration than in the trials. The committee in general prefers not to disassociate estimates of cost and effectiveness from a trial. However, it appreciated that many assumptions about caplacizumab's effectiveness in this model were not taken from the main trial. It also thought that some potential cost savings associated with caplacizumab may not have been included in the company's model.

## **To mitigate uncertainty around the modelling assumptions, a conservative approach is preferred**

3.20 The committee appreciated that the company made attempts to address uncertainty. However, it considered that several assumptions in the model remained uncertain and were at the more optimistic range of what

would be seen in clinical practice. It noted that, at the first committee meeting, the company had presented a deterministic ICER (which took a point estimate, or assumption for each model input) and a probabilistic ICER (which represented the average of many runs of the model using a range of values for each model input). The committee noted that these ICERs were similar, but the probabilistic analysis was incomplete because not all of the model inputs had a distribution around the deterministic value. This meant that not all of the uncertainty was accounted for in the probabilistic sensitivity analyses. The committee therefore considered a range of scenarios to test the effect of a range of plausible clinical outcome parameters on the ICER. On balance, it preferred assumptions that were more conservative than the company's base case. Although some uncertainty remained about these parameters, the committee noted that taking a more conservative approach reduced the risk that the ICER had been underestimated. Its preferred assumptions in the acute submodel were:

- a midpoint of 10% for the acute absolute mortality rates on standard care (that is, between 7% and 12.6%; see [section 3.10](#))
- a risk ratio for acute mortality rates for caplacizumab compared with standard care of 0.5 (see [section 3.12](#))
- utility values assuming 25% of the quality of life on standard care compared with caplacizumab. (see [section 3.18](#)).

The committee's preferred assumptions in the long-term Markov submodel were:

- the company's assumptions on prevalence of long-term complications on standard care (see [section 3.14](#))
- the company's revised standardised mortality ratio underlying the estimate of the absolute risk of dying for people on standard care (see [section 3.13](#))
- the effectiveness of caplacizumab compared with standard care reflecting long-term complications based on the association between time to platelet normalisation (estimated risk ratio of 0.66; see [section 3.15](#) and [section 3.16](#))
- an estimated risk ratio of death of 0.8 for caplacizumab compared with



standard care (see section 3.16)

- a lifetime duration of neuropsychological impairment (see [section 3.18](#))
- fear of relapse not modelled separately (see section 3.18)
- a relapse rate of 1.5% (see [section 3.17](#)).

Applying these assumptions and using a revised patient access scheme price discount for caplacizumab resulted in an ICER of £29,537 per quality-adjusted life year (QALY) gained.

## Caplacizumab is innovative

- 3.21 Caplacizumab is the first new treatment for acquired TTP in about 25 years with a different mechanism to the other drugs and treatments that form current standard care. Caplacizumab has additional benefits to standard care. The committee noted that there were benefits that may not have been captured in calculating the QALY. These included reducing the use of scarce NHS resources like plasma or intensive care unit beds. The committee concluded that caplacizumab is innovative.

## Conclusion

### Caplacizumab is a cost-effective use of NHS resources

- 3.22 The committee noted the considerable uncertainty around the estimates of cost effectiveness because of the limited clinical data, particularly around survival in the acute period and the long-term benefits of caplacizumab. It understood that the lack of data was, in part, because of the rarity of acquired TTP. Using the committee's preferred modelling assumptions resulted in an ICER of £29,537 per QALY gained. In line with the [NICE methods guide for technology appraisal](#), when a most plausible ICER is above £20,000 per QALY gained, the committee can take account certain factors, including innovation (see [section 3.21](#)). At its fourth meeting, the committee concluded that the ICER for caplacizumab fell within a range considered to be a cost-effective use of NHS resources and recommended caplacizumab as an option for treating acquired TTP.

## 4 Implementation

- 4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has acquired thrombotic thrombocytopenic purpura (TTP) and the doctor responsible for their care thinks that caplacizumab is the right treatment, it should be available for use, in line with NICE's recommendations.

## 5 Appraisal committee members and NICE project team

### Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee B](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes of each appraisal committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

### NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Mary Hughes**  
Technical lead

**Carl Prescott**  
Technical adviser

**Jo Ekeledo**  
Project manager

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