NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Caplacizumab for treating acute acquired thrombotic thrombocytopenic purpura

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using caplacizumab in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: June 2020

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using caplacizumab in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 26 June 2020

Second appraisal committee meeting: 16 July 2020

Details of membership of the appraisal committee are given in section 5

1 Recommendations

1.1 Caplacizumab with plasma exchange and immunosuppression is not recommended, within its marketing authorisation, 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.

1.2 This recommendation is not intended to affect treatment with caplacizumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For young people, this decision should be made jointly by them, their clinician, and their parents or carers.

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 may reduce the long-term complications of acquired TTP and risk of death around the time of an acute episode. But, the trial does not look at whether adding caplacizumab improves either length or quality of life over the long term. Alternative ways estimating these outcomes are not proven, so this needs confirming.

The limitations in the clinical evidence mean that the cost-effectiveness estimates for caplacizumab compared with standard care are very uncertain. However, they may be higher than the range normally considered a cost-effective use of NHS resources. So, caplacizumab is not recommended for treating acute acquired TTP.

Issue date: June 2020

2 Information about caplacizumab

Marketing authorisation indication

2.1 Caplacizumab (Cablivi, Sanofi) has a marketing authorisation for treating adults 'experiencing an episode of acquired thrombotic thrombocytopenic purpura, in conjunction with plasma exchange and immunosuppression'. On 30 April 2020, the European Medicines Agency's Committee for Medicinal Products for Human Use adopted a positive opinion recommending that a marketing authorisation extension is granted for caplacizumab for 'adolescents of 12 years of age and older weighing at least 40 kg'.

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). Costs may vary in different settings because of negotiated procurement discounts. The company has a commercial arrangement, which would have applied if the technology had been recommended.

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.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

- imbalances in the proportion of people who had rituximab between the arms of the HERCULES trial would not be expected to have a large effect on the cost-effectiveness estimates (issue 2, see technical report page 27)
- protocol violations in HERCULES would not be expected to have a large effect on the cost-effectiveness estimates (issue 3, see technical report page 29).

The company revised its base-case incremental cost-effectiveness ratio (ICER) during the technical engagement stage, and it was no longer over £30,000 per quality-adjusted life year (QALY) gained (issue 11, see technical report page 41).

The committee recognised that there were remaining areas of uncertainty associated with the analyses presented and took these into account in its decision making. It discussed issues 1, 4 to 10 and 12, which were outstanding after the technical engagement stage.

Current treatments and patient perspectives

Acquired thrombotic thrombocytopenic purpura (TTP) is a life-threatening condition associated with long-term morbidity and mortality

3.1 Acquired TTP is a rare autoimmune condition characterised by antibodies against ADAMTS13. This is an 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, hypertension and a shortened life expectancy. One clinical expert stated that acquired TTP is the most dangerous acute illness in haematology, with some people with the condition transitioning from showing no symptoms to death within hours. Although there are treatments for acquired TTP (see section 3.2), people can relapse. The patient experts explained that acquired TTP can have a big effect on quality of life and, in particular, on mental health. 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', people with the condition fear 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 48 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 are used to treat the underlying autoimmune condition, with the aim of limiting how many antibodies against ADAMTS13 are made. 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 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 aims to reduce blood clot formation during this time. The clinical experts explained that the longer blood vessels remained blocked, the higher the morbidity and mortality risk. 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 frequency (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 which reduce the duration and frequency 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 speciality 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 therefore treatment, may be delayed because many clinicians are unaware of aTTP, 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 aim is to have up to 9 specialist providers in England, providing clinical

expertise and geographical access for patients. If caplacizumab is recommended, some people could have it locally under remote supervision 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, treatment and patient outcomes. It concluded that a new NHS specialised service will attempt to reduce this and improve outcomes.

Clinical trial results

The main clinical trial, HERCULES, is broadly generalisable to UK clinical practice

3.5 HERCULES was a double-blind randomised controlled trial that included 145 people having an acute episode of acquired TTP. It 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). Caplacizumab's marketing authorisation states that it should be given before people start plasma exchange. However, in the trial, it was started after plasma exchange. This was because consenting and randomising patients threatened to delay plasma exchange, which was neither practical nor safe. One clinical expert stated that, in clinical practice, caplacizumab would be given 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 treatment effect. The trial included only 18 people from the UK. However, 1 clinical expert said that:

- the people in the trial, and treatments they had, reflected UK practice

- some of their patients have had caplacizumab for the last 2 years via a global compassionate use scheme
- the trial outcomes in the caplacizumab arm reflected the outcomes they had seen in NHS practice when using caplacizumab through the compassionate use scheme.

The committee concluded that HERCULES was generalisable to UK clinical practice.

The outcomes in HERCULES are clinically relevant, but do not test for short- or long-term morbidity or mortality

3.6 HERCULES measured clinical outcomes around an acute episode of acquired TTP. Data were collected while people were on treatment and for 28 days after they stopped treatment. The committee understood that an observational single-arm extension to HERCULES is ongoing. The primary outcome was time to platelet normalisation. However, people must have also stopped plasma exchange within 5 days of their platelet counts returning to normal. The committee noted that platelet count was a surrogate measure for more meaningful outcomes reflecting morbidity and mortality. The clinical experts explained that platelet count was an important outcome that was related to all other outcomes. The committee heard about (but did not see) evidence that the faster the platelet count is normalised, the lower the risk of complications. Key secondary outcomes in the trial in the company's statistical analysis plan were:

- a composite outcome of death, disease recurrence while on treatment and thromboembolic event
- disease recurrence alone
- the proportion of people whose condition did not respond to treatment.

Other secondary outcomes such as volume and duration of plasma exchange, time in hospital or intensive care, and death were not tested statistically. The clinical experts explained that all the measured

outcomes were clinically relevant. The patient experts said that plasma exchange use and time in hospital were 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 effect of caplacizumab on survival, quality of life, disability or mental health in the long term.

HERCULES shows that caplacizumab reduces plasma exchange use and hospital stays

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

- Caplacizumab reduced the time to 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 disease was controlled.
- Caplacizumab reduced the 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 (1 component of the composite outcome) during the acute period.
- Caplacizumab reduced the proportion of people having disease recurrence 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 mean duration of plasma exchange (6 days compared with 9 days on standard care alone), mean volume (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 experts explained that she had seen a similar reduction in number of plasma exchanges and hospital stay with caplacizumab when using caplacizumab through 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.

The company's economic model

The model structure is appropriate for decision making

3.8 The company separately modelled events around an acute episode of acquired TTP using a decision-tree model and events once a person had recovered from an acute episode using a Markov model. The decision-tree model was based on the data from HERCULES. In it, the company took into account the different rate of disease recurrence with caplacizumab and standard care alone in the 3 months after an acute episode. The company also modelled different probabilities of dying in the 2 treatment arms, not based data from HERCULES; but by doing a naive comparison of unpublished observational data (see section 3.9). The company used the Markov model to model for 55 years from the time a person recovered from an episode of acquired TTP. It modelled the same rate of disease relapse on caplacizumab and on standard care alone. It compared long-term cognitive impairment and mental health, and relapses and death for caplacizumab and standard care alone. The committee considered that the economic model captured relevant aspects of acquired TTP, and concluded that its structure was appropriate for decision making. However, it noted that the company populated its model mostly with evidence from observational data which was unadjusted both for potential confounders and for differences in the duration of the study determining mortality. It concluded that the treatment effects ascribed to

caplacizumab treatment in the model had not been validated (see sections 3.9 to 3.13).

During an acute episode of acquired TTP, the size of any association between treatment with caplacizumab and death is unclear

3.9 In HERCULES, 1 person randomised to caplacizumab died and 3 people randomised to standard care alone died. 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 the company could not use data from the trial to address whether caplacizumab prolongs life, the company presented a naive comparison of observational data for acute death in people who had treatment with or without caplacizumab to estimate the probability of dying in the acute period of the model. This approach included:

- For caplacizumab, a global compassionate use scheme in which clinicians requested caplacizumab from the company, who provided it free of charge (239 people had had treatment up to February 2020): One of the clinical experts stated that she requests caplacizumab for all her patients; the other clinical expert noted that less experienced centres may not have the same access to caplacizumab. The compassionate use scheme data suggested an absolute probability of dying on caplacizumab of 3.8% (9 deaths) over an equivalent period to the follow up in HERCULES (about 3 months after an acute episode).
- For standard care alone, the company did a meta-analysis of 129 international studies reporting the deaths around the acute episodein people who had standard care including plasma exchange. The company extracted the probability of dying during an acute episode, but did not adjust for the duration of the episode, or the year of the study. This analysis suggested an average' probability of dying of 13.2% during an acute hospitalisation. The committee noted that limited information was presented about: the populations in the study' how the meta-analysis addressed confounding; how well the study reflected

people in the UK with acquired TTP; and whether the meta-analysis accounted for changes in mortality over time. It also noted that the meta-analysis included studies with very heterogeneous results (probability of dying, 0 to 57%). It considered that restricting the analysis to 7 UK studies lowered the range of results and probability of dying. The committee's own analysis of the most relevant UK studies resulted in a probability of dying during an acute episode of around 7%.

The committee noted that the company had naively compared the data from these separate populations to estimate a relative risk for survival on caplacizumab compared with standard care alone of 0.29. This suggested that caplacizumab reduced the chance of death in the acute period by 71% compared with standard care alone. The company confirmed that it had not adjusted for any confounders, that is, characteristics of patients (or centres) that might be associated with having caplacizumab and also with dying. The committee's concern of confounding was supported by the clinical expert statement that there was an association between access to caplacizumab under the compassionate use programme and being cared for in a centre of excellence. The company stated that it did not have the necessary information to adjust for confounding. The committee thought it was biologically plausible that caplacizumab may reduce some deaths from an episode of acquired TTP. However, it questioned how the company meta-analysed the studies. It concluded that the possibility for confounding was high and that the analyses were not adequate to estimate the extent of benefit. The committee considered that the meta-analysis, if limited to contemporary studies generalisable to the UK, could be used to estimate an 'average' probability of dying around an acute episode for standard care. It concluded that having caplacizumab might reduce the risk of dying from an acute episode of acquired TTP. However, it concluded that the size of this reduction was unlikely to be as large as that estimated from unadjusted observational analyses, and remained uncertain.

The rates of long-term complications on standard care modelled by the company may not be generalisable to the UK

3.10 After recovering from a first episode of acquired TTP, people might have long-term complications arising from ischaemic damage (see section 3.1). In its Markov model, the company modelled death rate, and 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 who completed a survey rather than a random sample of people with acquired TTP.

To determine the risk of death in the longer term in people who had had standard care alone, the company used a standardised mortality ratio. This was the ratio of observed deaths after standard care divided by the expected number of deaths for the general population of similar age and gender. The committee considered that the company had not provided adequate information on the source of the deaths for people with acquired TTP treated with standard care alone. In particular, it did not think it was clear how generalisable the estimated death rate was to UK practice. The committee concluded that the company had not shown that the rates of long-term complications on standard care in its model were generalisable to the rates of these complications in current UK practice.

In the long term, there is no evidence that caplacizumab reduces the risk of complications

3.11 The committee considered whether caplacizumab prolonged life over the lifetime horizon of the model (see section 3.8). The company assumed that former treatment with caplacizumab reduced complications and extended life in the remission period above and beyond a benefit to mortality in the short term. 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. After estimating a risk of death for people on standard care (see section 3.10), 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 in the Markov model. 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. This meant that the company assumed that caplacizumab reduced the risk of long-term complications and death by 38% compared with standard care alone above and beyond acute effects. The committee noted that caplacizumab was not disease modifying, and would not be expected to work after people stopped having it. It understood that reducing exposure to blood clots, and so the likelihood of complications, in the short term would, in turn, reduce the risk of sequalae from these complications in the long 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 had not been validated, and that the company had not presented any clinical data. It recalled that the same proportion of people in each arm of HERCULES developed a major thromboembolic complication during short-term follow up in this trial. The committee was aware that some people might have pre-existing complications before having caplacizumab, which might also

prolong stay in hospital and which the drug would not improve or cure. The committee concluded that it was not possible to validate a causal link between former treatment with caplacizumab and long-term complications based on the evidence provided by the company.

Modelled rate of relapse is low, and it is uncertain whether caplacizumab works equally well when reused

3.12 The committee appreciated that someone could have caplacizumab 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 concluded the relapse rate was likely to be higher than 1% in clinical practice, and that it was uncertain whether caplacizumab was as effective on reuse compared with initial use.

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

3.13 There were no quality-of-life data collected in HERCULES. The company instead used quality-of-life data from people who were 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, in their opinion, this did not reflect how severely an acute episode affected people. The committee noted that a company scenario which assumed a greater effect on quality of life had only a small effect on the company's cost-effectiveness estimates. It also noted that quality-of-life estimates for acquired TTP

should include an estimate of the fear of relapse. This was because people with the condition stated this affected their mental health (see section 3.1), not because caplacizumab would lessen relapse, but because they would know a treatment exists. The committee noted that the company had estimated the quality of life associated with cognitive impairment and mental health in the long term based on studies in people with stroke and people with depressive disorder respectively. It acknowledged that cognitive impairment and mental health would lower a person's quality of life. However, it recalled that there was no evidence that caplacizumab would decrease the likelihood of having these complications or improve quality of life by decreasing these complications of acquired TTP (see section 3.11). The committee concluded that the effect of acquired TTP on quality of life is considerable but uncertain, and that the effect of alternative quality-of-life assumptions should be explored further.

The estimates for cost effectiveness from the company and the ERG do not account for uncertainty around assumptions

3.14 The company's and ERG's base-case cost-effectiveness estimates were similar (£28,000 and £31,000 per QALY gained respectively). The ERG's base case used the company assumptions both for the probability of dying in the short-term (see section 3.9) and for estimating the long-term complications and death rate (see sections 3.10 and 3.11). The ERG explained that it had not varied the company's assumptions because there were a range of sources for short-term mortality presented by the company, all of which were consistent. It also thought that it was biologically plausible to assume an effect. The committee noted that:

- the size of association from epidemiological evidence relating caplacizumab treatment with better outcomes was potentially highly biased
- the company did not validate the surrogate endpoints it chose to reflect long-term complications

- all the approaches suggested by the company were associated with high levels of uncertainty
- the model was highly sensitive to the company's assumptions.

This meant that it was essential that the company and ERG explored uncertainty around varying these assumptions, including the possibility of no effect. The committee considered that caplacizumab might reduce short-term deaths around an acute episode. However, it thought that the limitations of the data meant the extent of the survival benefit was unclear. Any evidence for a benefit of caplacizumab on long-term complications and acquired TTP-related death was even more limited. The clinical experts stated that this meant it was not possible to say whether the estimates in the company's model were plausible. The committee further noted that:

- Assuming no survival benefit in the short term around an acute episode and no survival benefit in the long term resulted in an ICER of around £120,000 per QALY gained. Assuming no benefit of caplacizumab on the rate of long-term complications such as cognitive impairment and mental health issues compared with standard care increased this further.
- Accepting the company's estimate of short-term survival benefit but assuming no survival benefit in the long term resulted in an ICER of around £47,000 per QALY gained. Assuming no benefit of caplacizumab on reducing long-term complications increased this further.

The committee concluded that neither the company's nor the ERG's cost-effectiveness estimates accounted for the uncertainty around the assumptions in the economic model, particularly those around death rates.

Steps are needed to address remaining uncertainties

3.15 The committee agreed that the company would need to address the following uncertainties before it could further assess the potential cost effectiveness of caplacizumab:

- Estimates of the probability of dying around an acute episode:
  - The meta-analysis of the probability of dying for standard care alone around an acute episode of acquired TTP (see section 3.9) should reflect current UK practice using studies from the UK only, or those most relevant to UK clinical practice.
  - The estimate of deaths oncaplacizumab around an acute episode should provide information on the setting in which people had treatment and how generalisable these data are to a UK population.
  - The indirect comparison of probability of dying around an acute episode of acquired TTP (see section 3.9) should provide clear methods, adjust for confounding, discuss how residual confounding may have biased the results and justify the size of any mortality benefit assumed.
  - The estimates should be put into context in terms of interventional trials of other treatments for acquired TTP, with mortality as the outcome.
- Estimates of caplacizumab's long-term treatment effect:
  - Data should be included for long-term morbidity and mortality on current standard care for the UK population, particularly for serious organ damage.
  - The relationship between intensive care or hospital stay and long-term outcomes for people with acquired TTP should be validated.
  - If data are not available, other short-term outcomes should be used to model the treatment effect of caplacizumab compared with standard care alone on long-term outcomes. The relationship between the short- long-term outcomes should be fully justified and validated.

  - When possible, the modelled rates of long-term complications with caplacizumab and standard care alone should be compared with observed data.
  - Scenarios in which former treatment with caplacizumab does not extend life and in which caplacizumab does not extend life or reduce complications should be considered in the Markov portion of the model.
- Utility values:
  - Alternative quality-of-life scenarios, including the modelling of worse quality of life during an acute episode of acquired TTP (see section 3.11) should be provided.
- Scenario analyses:
  - A range of scenarios including conservative assumptions on the relative risk of short- and long-term mortality and long-term complications should be presented.

Caplacizumab is innovative but the extent to which it is a step change in treatment remains unclear

3.16 Caplacizumab is the first new treatment for acquired TTP in about 25 years. It has a different mechanism of action to the other drugs and treatments that form current standard care. Caplacizumab has additional benefits to standard care. However, the committee thought the extent to which it is a step change in the treatment of acquired TTP was unclear because of the uncertainty about its effect on overall survival and long-term complications. It noted that there were benefits which may not have been captured in the QALY calculation such as:

- the effect of caplacizumab in reducing plasma exchange duration on the number of central lines replacements a patient would need, how this reduces the risk of infection and how this would affect a patient's quality of life
- the effect that knowing another treatment exists would have on anxiety

- the broader positive effect on the NHS of reducing the use of scarce NHS resources, such as plasma.

Overall, the committee concluded that caplacizumab is likely innovative, but the extent to which it is a step change in treatment for acquired TTP remained unclear.

Further data collection through a managed access agreement could reduce the risk to the NHS

3.17 The committee was aware that NICE has published guidance that includes time-limited managed access agreements. These are temporary commercial agreements to manage high-level clinical uncertainty while collecting data from ongoing trials and NHS clinical practice to resolve these uncertainties before a NICE review. The committee considered that a managed access arrangement could reduce the risk to the NHS in this case. It recognised that a managed access agreement needs NHS England and Improvement, NICE, the company and relevant data holders to sign up to it. The committee concluded that the feasibility of a managed access agreement should be explored using the committee's preferred assumptions around modelling.

Because of the uncertainty in the clinical and economic evidence it is not possible to determine an acceptable ICER

3.18 NICE's guide to the methods of technology appraisal notes that above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. It states that a committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. Because of the high level of uncertainty in the clinical and economic evidence for caplacizumab, the committee agreed that it was not possible to determine an acceptable ICER.

Conclusion

Caplacizumab is not recommended for an acute episode of acquired TTP

3.19 The committee stated that neither the company's nor the ERG's cost-effectiveness estimates accounted for the uncertainty around the assumptions in the economic model, particularly those around death rates and risk of long-term complications. It considered that caplacizumab may reduce the chance of death around an acute episode but the extent of the benefit was unclear. There was even less evidence to support reduced long-term complications with caplacizumab used around an acute episode compared with standard care alone. Given the uncertainty, the committee considered that it was appropriate to use more conservative assumptions for benefits on mortality and long-term complications with caplacizumab compared with standard care alone than those in the company base case. It noted that doing this would increase the ICER. The committee concluded that it was not possible to determine the most plausible ICER for caplacizumab compared with standard care alone. However, it concluded that using more conservative assumptions would increase the ICER above the range considered to be a cost-effective use of NHS resources.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Professor Amanda Adler

Appraisal Committee

June 2020

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.

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