

# caplacizumab 10mg powder and solvent for solution for injection (Cablivi®)

Sanofi

07 August 2020

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

**ADVICE:** following a full submission

**caplacizumab (Cablivi®)** is accepted for use within NHSScotland.

**Indication under review:** Treatment of adults experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression.

Caplacizumab, compared with placebo, decreased the time to platelet count response and reduced the risk of thrombotic thrombocytopenic purpura recurrence in adults receiving plasma exchange and immunosuppression for aTTP.

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

**Chairman**  
**Scottish Medicines Consortium**

## Indication

Treatment of adults experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression.<sup>1</sup>

## Dosing Information

Initially caplacizumab 10mg intravenous (IV) injection given prior to plasma exchange for the first dose. Subsequent doses of caplacizumab 10mg subcutaneous (SC) injection given daily after completion of each plasma exchange for the duration of daily plasma exchange treatment, followed by a further 30 days of caplacizumab 10mg SC injection daily. If, at the end of this period, there is evidence of unresolved immunological disease, it is recommended to optimise the immunosuppression regimen and continue daily caplacizumab 10mg SC administration until the signs of underlying immunological disease are resolved (for example, sustained normalisation of ADAMTS13 activity level). In the clinical development program, caplacizumab has been administered daily for up to 65 days. No data on re-treatment with caplacizumab are available.

Treatment with caplacizumab should be initiated and supervised by physicians experienced in the management of patients with thrombotic microangiopathies.<sup>1</sup>

## Product availability date

June 2019

Caplacizumab has been designated an orphan medicine for the treatment of TTP by the European Medicines Agency (EMA).

## Summary of evidence on comparative efficacy

Caplacizumab inhibits the interaction between von Willebrand Factor (vWF) and platelets thereby preventing platelet adhesion mediated by ultra-large vWF (UL-vWF) multimers, which are present in aTTP. In this autoimmune disorder inhibitor autoantibodies to ADAMTS13 produce a deficiency of this vWF-cleaving enzyme leading to accumulation of UL-vWF multimers that bind to platelets and induce adhesion. Consumption of platelets into the microthrombi causes thrombocytopenia.<sup>1</sup>

A double-blind phase III study (HERCULES) recruited adults with aTTP, which required plasma exchange treatment, who had received only one plasma exchange prior to randomisation. Patients were randomised equally, with stratification by Glasgow Coma Scale (GCS) score ( $\leq 12$  or 13 to 15), to caplacizumab 10mg intravenously before the first plasma exchange after randomisation (which had to start within 24 hours of previous plasma exchange) then caplacizumab 10mg subcutaneously daily until 30 days after the end of plasma exchange treatment or placebo, with the option to continue therapy for an additional 28 days if required. Patients who had a recurrence, defined as a new decrease in platelet count necessitating re-initiation of plasma exchange after normalisation of the platelet count had occurred, could receive open-label caplacizumab. All patients received daily plasma exchange until at least 2 days after platelet count

normalisation. Also glucocorticoids (prednisone or prednisolone dose of  $\geq 1$  mg/kg/day) were administered during and for at least a week after plasma exchange, with dose tapering at investigator's discretion to aim for completion of glucocorticoid treatment within 30 days after last plasma exchange. Other immunosuppressive therapy (for example, rituximab) was permitted at the investigator's discretion. At the end of study drug treatment patients were followed-up for an additional 4 weeks. The primary outcome was time from first dose of study drug to platelet count response, defined as a platelet count  $\geq 150 \times 10^9/L$  with subsequent discontinuation of plasma exchange within 5 days. This was assessed in the intent-to-treat (ITT) population, which comprised all randomised patients.<sup>2,3</sup>

Caplacizumab, compared with placebo, significantly reduced time to platelet count response. This is detailed in Table 1, which also described results for the four key secondary outcomes tested in a hierarchical strategy in the order listed in the table. There was no formal testing after the first non-significant outcome in the hierarchy, which was observed for the third secondary outcome. Caplacizumab, compared with placebo, significantly decreased the proportion of patients who had an event within the first secondary outcome, which was a composite of TTP-related death, TTP recurrence or major thromboembolism during the study treatment period. This was mainly due to a reduction in TTP recurrence (4.2% versus 38%) and TTP-related deaths (0 versus 4.2%), with 8.5% and 8.2% of patients in the respective groups having a major thromboembolism. Similarly, the second secondary outcome, proportion of patients who had TTP recurrence during the overall study period (including 4-week follow-up), was significantly lower with caplacizumab.<sup>2,3</sup>

**Table 1: Primary and secondary outcomes of HERCULES study.**<sup>2,3</sup>

	Caplacizumab	Placebo	
	N=72	N=73	p-value
<b>Primary outcome: time to platelet count response</b>			
Events	66	66	
Median (days)	2.69	2.88	
Hazard ratio (95% confidence interval)	1.55 (1.09 to 2.19)		0.01
<b>Key Secondary Outcomes</b>			
TTP-related death, TTP recurrence or major thromboembolism during treatment, <sup>A</sup> n (%)	9 (12%)	36 (49%)	<0.001
TTP recurrence during treatment and follow-up, <sup>B</sup> n (%)	9 (12%)	28 (38%)	<0.001
Refractory TTP, <sup>C</sup> n (%)	0	3 (4.2%)	0.06
Median time to normal organ-damage markers (days)	2.86	3.36	
<b>Additional Secondary Outcomes</b>			
Median duration of plasma exchange (days)	5	7	
Median duration in ICU (days)	3	5	
Median duration in hospital (days)	9	12	

#TTP = thrombotic thrombocytopenic purpura; A = during the study drug treatment period; B = during the overall study period including 4-week follow-up. Analyses of the first two key secondary outcomes did not include data after any switches to open-label caplacizumab. C = recurrence was defined as a new decrease in the platelet count that necessitated the re-initiation of plasma exchange after normalisation of the platelet count had occurred. Refractory TTP = absence of a doubling of the platelet count after 4 days of treatment and a lactate dehydrogenase (LDH) level that remained above the upper limit of the normal range. Analysis of additional secondary outcomes included data from the overall study period including open-label caplacizumab with patients analysed according to their initial assigned treatment group.

A single-blind phase II study (TITAN) was stopped early due to low recruitment and there were a number of conduct issues that limited its internal validity and interpretation of results. Although, this prevented inclusion in the summary of product characteristics (SPC), it was considered by the European Medicines Agency (EMA) that it had demonstrated proof-of-concept and was supportive of the phase III study.<sup>2</sup> The study recruited 75 adults with an acute episode of aTTP who required plasma exchange. They were equally randomised to the licensed dose of caplacizumab or placebo in combination with plasma exchange and standard immunosuppression. The primary outcome was time to confirmed normalisation of platelet count response, defined as a platelet count  $\geq 150 \times 10^9/L$  maintained at or above this level after 48 hours and lactate dehydrogenase (LDH)  $\leq$  twice the upper limit of normal. This was significantly reduced with caplacizumab, compared with placebo, with an event rate ratio of 2.2 (95% CI: 1.28 to 3.78),  $p=0.005$ . In the caplacizumab and placebo groups, median time to response was 3.0 versus 4.9 days within the 69 patients who had not received a plasma exchange prior to enrolment and was 2.4 versus 4.3 days within the 6 patients who had plasma exchange prior to enrolment. The secondary outcome, TTP exacerbation rate (defined as a new plasma exchange-requiring episode of thrombocytopenia between 1 and 30 days after the last plasma exchange session), was reduced in the caplacizumab group compared with placebo: 8.3% versus 28%.<sup>2,4</sup>

### Summary of evidence on comparative safety

In the HERCULES study the median duration of treatment in the caplacizumab group was 35 days (range 1 to 65) and in the placebo group was 23 days (range 2 to 66). Any treatment-emergent adverse event was reported by 97% (69/71) of patients in the caplacizumab group and 97% (71/73) in the placebo group and these were considered treatment-related in 58% and 44% respectively. If adverse events of TTP were excluded 96% and 90% of patients in the respective groups had a treatment-emergent adverse event. In the caplacizumab and placebo groups serious adverse events were reported by 39% versus 53%, and these were treatment-related in 14% and 5.5%, respectively. Adverse events leading to discontinuation of study drug were reported by 7.0% versus 12% of patients in the respective groups.<sup>2,3</sup>

As caplacizumab interferes with vWF, a key protein in haemostasis, it can be associated with mucocutaneous bleeding that is similar to that observed in patients with von Willebrand's disease. Bleeding-related adverse events were the most frequently reported and occurred at a higher rate in the caplacizumab group, compared with placebo, 65% versus 48% of patients, with epistaxis reported by 32% versus 2.7%, and gingival bleeding by 18% versus 1.4%. The majority were mild or moderate. However, 3 patients in the caplacizumab group had severe bleeding adverse events (epistaxis, gingival bleeding, and upper gastrointestinal haemorrhage in 1 patient each) and 1 patient in the placebo group had a haemorrhagic transformation stroke. Serious adverse events of bleeding were reported by 11% (8/72) and 1.4% (1/73) of patients in the caplacizumab and placebo groups. The most commonly reported serious adverse event of bleeding was epistaxis, which occurred in 4 caplacizumab-treated patients. Other common adverse events that occurred at a higher rate in the caplacizumab group, compared with placebo, included headache (22% versus 8.2%), urticaria (17% versus 6.8%), dyspnoea (9.9% versus 2.7%), fatigue (14% versus 8.2%),

pyrexia (14% versus 8.2%) and viral upper respiratory tract infection (5.6% versus 0). Adverse events reported at a lower rate in the caplacizumab group, compared with placebo, included hypokalaemia (8.5% versus 19%) and rash (7.0% versus 12%).<sup>3</sup>

In the TITAN study treatment-emergent adverse events were reported in the caplacizumab and placebo groups by 97% (34/35) and 100% (37/37), respectively, (TTP were excluded from this analysis). These were considered treatment-related in 57% and 14% respectively. Serious adverse events were reported by 57% versus 51%, and were treatment-related in 20% and 0, respectively. Adverse events lead to study drug discontinuation in 11% versus 5.4% of patients in the respective groups. Bleeding-related adverse events were more common in the caplacizumab group, compared with placebo: 54% versus 38%. The most common bleeding-related adverse events with caplacizumab were epistaxis (31%), gingival bleeding (14%), bruising (11%), petechiae (11%), and haematoma (11%), all with mild to moderate severity. One subarachnoid haemorrhage was reported for caplacizumab, and one cerebral haemorrhage (fatal) and one haemorrhagic stroke in the placebo arm. Two patients experienced a serious bleeding-related adverse that was considered at least possibly related to caplacizumab: subarachnoid haemorrhage and metrorrhagia, respectively. Immune-related adverse events were more common in the caplacizumab group, compared with placebo: 49% (17/35) versus 32% (12/37).<sup>2,4,5</sup>

## Summary of clinical effectiveness issues

Caplacizumab is the first medicine to be licensed for aTTP and has been designated as an orphan medicine by the EMA.

aTTP is a rare life-threatening, autoimmune blood clotting disorder caused by autoantibodies that inhibit ADAMTS13, resulting in a severe deficiency of this vWF-cleaving protease enzyme. This leads to accumulation of UL-vWF multimers that bind to platelets and induce adhesion. Consumption of platelets into these micro thrombi causes severe thrombocytopenia and the widespread formation of microvascular thrombi can lead to tissue ischaemia and organ dysfunction, commonly involving the brain, heart and kidneys. Acute thromboembolic events may occur, such as stroke, myocardial infarction and venous thrombosis. With current treatment aTTP has been reported to be fatal in 20% of patients with most deaths occurring in the first month and a median time to death of 9 days. In addition to the acute risks, patients may have long-term consequences such as cognitive deficits, depression and arterial hypertension. They also have a risk of aTTP recurrence, with reported rates ranging from 10% to 84%. These typically occur within 1 or 2 years but recurrences have been reported up to 30 years after the initial episode. Currently aTTP is managed with plasma exchange and immunosuppression with corticosteroids and sometimes rituximab.<sup>2,6</sup> Clinical experts consulted by SMC note that rituximab is generally used for severe or refractory cases. Clinical experts consulted by SMC considered that caplacizumab fills an unmet need in this therapeutic area, particularly because it offers improved outcomes to patients with a life-threatening condition.

In the HERCULES study caplacizumab, compared with placebo, significantly reduced the time to platelet count response (HR 1.55), with the effect most evident in late responders. The EMA noted that a shorter time to platelet response is considered of clinical relevance as it reduces the time at

the highest risk for morbidity and leads to shorter primary exposure to plasma exchange and the procedure-associated risks. Caplacizumab also reduced the duration of plasma exchange and time spent in hospital, including time spend in intensive care unit (ICU). Caplacizumab also significantly reduced the proportion of patients with the composite secondary outcome during study drug treatment period that included TTP-related death, TTP recurrence and major thromboembolic events (12% versus 49%), with effects mainly due to a reduction in TTP recurrence (4.3% versus 38%). Similar significant effects with caplacizumab on TTP recurrence over the whole study period (treatment and follow-up) were also observed (12% versus 38%). The EMA considered the reduction in risk of recurrence to be clinically relevant.<sup>2,3</sup>

The dosing regimen in the HERCULES study differs from the licensed regimen in the timing of the first dose of caplacizumab. The SPC indicates that this should be given before the first plasma exchange. However, in the HERCULES study it was administered after the first plasma exchange. Dosing during the phase II TITAN study was more representative of the licensed regimen as the majority of patients received caplacizumab before their first plasma exchange. However, as noted previously there were issues with the conduct of the TITAN study limiting its internal validity and interpretation of results.<sup>1-4</sup>

Patients in the HERCULES study who had a recurrence during the study drug treatment period were switched to open-label caplacizumab. This may complicate the interpretation of some results after the double-blind phase. Also, there were some differences across the treatment groups in concomitant immunosuppressant medicines and treatments. Within the caplacizumab and placebo groups corticosteroids were given to 96% and 97% of patients and rituximab to 39% and 48% of patients, respectively. Rituximab tended to be commenced later in patients within the caplacizumab group than in the placebo group. Use of other immunosuppressant medications and treatments, mainly mycophenolate mofetil (8.3% versus 0), was higher in the caplacizumab group.<sup>2,3</sup>

In the caplacizumab and placebo groups TTP recurrence was experienced by 3 and 28 patients within the 30 days of the end of plasma exchange (“exacerbation”) and by 6 and 0 patients during follow-up (“relapse”). All 3 caplacizumab-treated and 25 of the placebo-treated patients who had an exacerbation had ADAMTS13 <10%, indicating unresolved underlying autoimmune disease. All 6 caplacizumab-treated patients who had a relapse also had ADAMT13 <10% when study drug treatment was stopped.<sup>3</sup> The SPC advises that after the initial treatment period of 30 days post-plasma exchange is complete, if there is evidence of unresolved immunological disease, the immunosuppression regimen should be optimised and caplacizumab continued until the signs of underlying immunological disease are resolved (for example, sustained normalisation of ADAMTS13 activity level). However, it also noted that in the clinical development program, caplacizumab has only been administered for up to 65 days.<sup>1</sup>

There was no evidence relating to re-treatment with caplacizumab for a second or subsequent episode of aTTP. Information on this may be provided by the ongoing Post-HERCULES study which is expected to complete in October 2020.

The company noted that HERCULES used the International Consensus definition for relapse, which is a reduction in platelet count requiring re-initiation of plasma exchange that occurred more than 30 days after completion of plasma exchange treatment. However, as the study only provided a

short follow-up, clinical opinion is that relapses in the study were late exacerbations rather than true relapses when the latter is considered a disease recurrence following a prolonged period of disease stabilisation.

Clinical experts consulted by SMC consider that caplacizumab is a therapeutic advance in the treatment of aTTP due to its improvement in platelet response time and clinical outcomes. They consider that caplacizumab would be added to current standard treatment with plasma exchange and immunosuppression and suggest that it may be used in severe or refractory cases of aTTP.

## Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing caplacizumab plus standard care (SoC) versus SoC alone for the treatment of acute aTTP episodes. Current standard of care (SoC) is plasma exchange (PEX) therapy and immunosuppression. Base case analysis was provided for the entire disease population. The time horizon for the analysis was 55 years.

A decision tree model was used to model the acute episode while a cohort-level Markov model structure was used to model aTTP in remission. The decision tree model captured possible patient pathways and short-term outcomes over the acute aTTP episode. Patients entered the model after experiencing an acute episode of aTTP and from there they either receive caplacizumab plus SoC or SoC alone. Subsequently, patients either respond to treatment or have refractory disease. Thereafter, patients may or may not experience an exacerbation and subsequently they either die or transition into the Markov model in the remission state.

The Markov model tracks patients following an acute episode of aTTP for their remaining lifetime. It is split into three main health states corresponding to remission, relapse and death. Relapse in Markov model is referred to as 'true relapse' and should not be confused with relapse as per HERCULES trial. In the model, patients can transition from remission to dead or from remission to true relapse. Patients who do not die or relapse remain in the remission health state and the model assumes that patients can only relapse following a period of remission which is consistent with the clinical definition of relapse. While in the remission state following an acute aTTP episode, patients could experience a number of long-term complications, of which cognitive impairment and neuro-psychological impairment (encompasses depression, anxiety and PTSD conditions) were included in the model. As such then, patients in remission health state were expected to reside in one of the four sub-states i.e. without any chronic conditions, with cognitive impairment, with neuro-psychological impairment, or both impairments combined. A cycle length of 3 months is used for the Markov model, reflecting the relatively stable condition of patients with aTTP in remission.

The clinical effectiveness parameters for caplacizumab were estimated from a phase III clinical study (HERCULES) but supplemented by external literature sources or clinical expert opinion where there was paucity of data or the evidence was not reflective of current practice in UK. The decision tree model for acute phase used data obtained from HERCULES trial to estimate the proportion of patients with refractory disease and the risk of early and late exacerbations. However, for acute mortality estimates, due to lack of realistic values from the trial, data were

derived from a combination of literature sources, caplacizumab compassionate use program and clinical expertise/opinion. Similarly, for the Markov model as HERCULES did not investigate long-term complications (cognitive and neuro-psychological impairment), mortality in remission or true relapse rate, all model inputs were informed by assumptions made on the basis of literature sources and clinical opinion. Key amongst these assumptions were the RR of 0.62 used for long-term complications (both cognitive and neuro-psychological impairment of different severity) and mortality in remission in patients treated with caplacizumab versus SoC and the estimated true relapse rate of 1% for both caplacizumab and SoC treated patients.

The economic analysis incorporated resource use and quality of life decrements associated with serious adverse events (SAEs) occurring in > 5% of patients in either treatment arm of the HERCULES trial plus certain AEs occurring < 5% such as serious PEX complications (deep vein thrombosis and line infections). These were included (based on clinical opinion) in the vascular disorders and infections/infestations system/organ classes respectively.

Given the severely disabling condition during an acute aTTP episode, health-related quality of life (HRQoL) data were not collected in HERCULES study. Hence, utility estimates for patients at different time points during an acute aTTP episode i.e. before the episode, during hospitalisation and after discharge were estimated by using age and sex matched general population utility from HERCULES patient-level data and subsequently applying utility multipliers to this value obtained from surrogate literature sources. For instance, baseline utility derived from HERCULES patient-level data before an aTTP episode was calculated to be 0.87 but after applying utility multipliers denoting change in utility during hospitalisation or post-discharge, the average utility for acute aTTP episode dropped down to 0.67-0.72 and 0.63-0.70 for patients on caplacizumab and SoC respectively. The range of utilities denote difference in experiencing an acute episode depending on if a patient responds to a treatment or has refractory disease and someone who exacerbates or not in both situations.

Similarly for patients in remission, relevant baseline utility estimates and utility decrements were sourced from literature which were then used to generate health state specific utility multipliers. These multipliers are then applied to baseline utility value of 0.77 for patients in remission (without any chronic conditions) and result in specific health state utility estimates during each Markov cycle which then sum up to provide an accrued QALY value for that particular health state in each treatment arm.

Furthermore, adverse event disutilities were also sourced from searches of previous NICE appraisals and literature sources due to no clinical data being readily available. A scenario analysis was also provided to incorporate carer effects.

Acquisition and administration costs for caplacizumab and all comparators were included in the analysis, as were the costs associated with any subsequent additional medicine or resource use and background disease management costs.

A Patient Access Scheme (PAS) was proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a discount on the list price for caplacizumab has been offered. The base case result are shown in table 2.

Table 2: Base case results, with PAS

Technologies	Total LYs	Incremental LYs	ICER incremental (£/QALY)
SoC	16.23		
Caplacizumab	21.99	5.76	£27,972

**Key:** ICER, incremental cost-effectiveness ratio; LY, life years; PAS, patient access scheme; QALY, quality-adjusted life year; SoC, standard of care.

In one way sensitivity analysis the model was most sensitive to the relative risk (RR) for mortality in remission, treatment duration days during the double-blind period, annual true relapse rates and the RR of experiencing long-term mild cognitive impairment for caplacizumab, as shown in table 3. These individually or in combination pose a high level of uncertainty associated with extrapolation of clinical efficacy to long term costs and benefits for caplacizumab. A range of scenario analyses were performed, with the potentially most plausible scenarios presented in Table 4 below. The scenario analyses which had the greatest upward impact on the ICER for caplacizumab was the alternative acute mortality rate based on HERCULES ITT data, reduced time horizon and annual probability of true relapse.

Table 3: One way sensitivity analysis results for the top 4 most influential parameters, with PAS

Parameters	Base case value	Upper bound value	ICER (upper limit)
Mortality in remission, RR caplacizumab	0.62	0.75	£33,002
True relapse, annual probability	1%	4%	£32,584
Treatment duration (days), caplacizumab patient double blind period	36.6	40.3	£31,134
RR mild cognitive impairment, caplacizumab	0.62	0.75	£29,979

Table 4: Scenario analysis results with PAS

	Scenario	Base case	ICER	Difference from baseline
	Base case ICER	-	£27,972	-
1	Subgroup with ADAMTS13 activity < 10%	HERCULES ITT	£27,427	-£545
2	Annual probability of true relapse, 2% per annum	1%	£30,147	£2,175
3	Source for baseline cognitive impairment % SoC: Cataland (2011)	Kennedy (2009) <sup>7</sup>	£28,487	£515
4	Assume that all patients experience long-term complications	As per literature sources	£25,375	-£2,597
5	Acute mortality based on HERCULES ITT data	UK expected mortality	£32,132	£4,160
6	Mortality source in remission: Deford (2013)	Upreti (2019) <sup>8</sup>	£28,539	£567

	Scenario	Base case	ICER	Difference from baseline
7	QALY modifier: 1.7	No QALY weighing applied	£16,424	-£11,548
8	Include caregiver QoL?: Yes	No	£27,570	-£402
9	Include wastage when costing rituximab? No	Yes	£27,947	-£26
10	Include costs for treating AEs?: Yes	No	£28,070	£98

**Key:** AE, adverse event; aTTP, acquired thrombotic thrombocytopenic purpura; ICER, incremental cost-effectiveness analysis; ITT, intention-to-treat; PAS, patient access scheme; PEX, plasma exchange; QALY, quality-adjusted life year; QoL, quality of life; RR, relative risk; SoC, standard of care.

The economic analysis was associated with a number of weaknesses and uncertainties:

- The primary reason for uncertainty in the model stems from the lack of clinical evidence for some short-term and almost all long-term costs and benefits derived when caplacizumab is used with SoC.
- No direct or high-quality literature based evidence was available to confirm the utility and disutility values associated with aTTP as an acute episode or in remission. Most values were derived from a mix of literature and proxy sources using utility multipliers which give rise to uncertainty, especially in case of long term complications (cognitive and neuro-psychological impairment), something that is highlighted in OWSA.
- Specifically with regards to the acute phase (decision tree), there is uncertainty around acute mortality rates for aTTP patients on caplacizumab or SoC as no high quality data is available to confirm the values as most of it relies either on clinical expertise or observational data obtained from compassionate use program. The impact of variation for this parameter can be seen in OWSA and scenario analysis based on HERCULES ITT data in table 4.
- In terms of remission phase (Markov model), there is uncertainty around annual true relapse rate and relative risks (RR) for mortality in remission and suffering from long term complications such as cognitive and neuro-psychological impairment as all of these were derived exclusively from a mix of literature sources and clinical opinion. OWSA highlighted the sensitivity around these assumptions as they had the maximum influence on base case ICER.
- To estimate long terms costs, resource use frequencies and proportion of patients using each resource was exclusively estimated from a healthcare resource survey which can potentially bias the values estimated. OWSA again highlighted the sensitivity around this parameter.
- Due to these uncertainties further scenario analyses and probabilistic sensitivity analyses were requested and they did help demonstrate the degree of uncertainty with respect to the probability of caplacizumab being cost-effective. The results showed that at a WTP threshold of £20,000 caplacizumab had only a 1.3% probability of being more cost-

effective than SoC, however at £30,000 threshold it has a 70.2% chance, while at £40,000 threshold it has 98.9% chance of being more cost-effective than SoC.

Despite the issues stated above, the economic case was considered to be demonstrated.

Other data were also assessed but remain confidential.\*

## Summary of patient and carer involvement

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

- We received patient group submissions from TTPNetwork and Thrombosis UK, both organisations are registered charities.
- TTPNetwork has not received any pharmaceutical company funding in the past two years. Thrombosis UK has received 15% pharmaceutical company funding in the past two years including from the submitting company.
- Acquired thrombotic thrombocytopenic purpura (aTTP) is a rare blood disorder. Clots form in small blood vessels with risk of organ damage and stroke. Sudden and severe onset of symptoms requires urgent medical treatment to prevent death and reduce the risk of organ damage. There is a lifetime risk of relapse. People experience constant fatigue, 'brain fog', debilitating anxiety over risk of relapse and constantly monitor for changes in health, energy and bruising. Family and work life is impacted with individuals reducing working hours or changing jobs and regular support and care is required.
- Current treatments including rituximab and prednisolone can take time to raise platelet levels. Plasma exchange is effective but takes several hours and causes nausea and fatigue. Receiving donor blood may also not be favoured by some patients.
- caplacizumab (Caplivi) is innovative, less invasive and the first advance in treatment for over 25 years. Administered by sub-cutaneous injection, it acts quickly, reduces risk of serious harm or death, is well tolerated and there are fewer incidences of relapse. People can return to work or family activities quicker.
- Few side effects are experienced although needle phobia can exist.

## Additional information: guidelines and protocols

In 2012 the British Committee for Standards in Haematology (BCSH) published guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. For treatment of acute TTP, it recommends that daily plasma exchange is the mainstay of therapy and should be started as soon as possible after diagnosis. Immediately after plasma exchange corticosteroids should be started with either methylprednisolone (1g IV per day for 3 days) or oral prednisolone (1mg/kg/day) with an oral proton pump inhibitor. Oral folic acid 5 mg daily should also be given.<sup>6</sup>

## Additional information: comparators

It is expected that caplacizumab would be added to current standard treatment with plasma exchange and immunosuppression.

## Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per course (£)
Caplacizumab	10mg IV on day one, then 10mg SC daily continued until 30 days after completion of plasma exchange	145,005

*Costs from BNF online on 24.02.20. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take patient access schemes into consideration. Costs based on caplacizumab median duration of treatment of 35 days in the phase III HERCULES study.*

## Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 15 patients in each year and 10 patients to be treated in year 1 rising to 11 patients in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

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

## References

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7. Kennedy AS, Lewis QF, Scott JG, et al. Cognitive deficits after recovery from thrombotic thrombocytopenic purpura. *Transfusion.* 2009; 49(6):1092-101.
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This assessment is based on data submitted by the applicant company up to and including 17 July 2020.

*\*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: [http://www.scottishmedicines.org.uk/About\\_SMC/Policy](http://www.scottishmedicines.org.uk/About_SMC/Policy)*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*