5.04 CAPLACIZUMAB, Injection set containing 1 vial powder for injection 10 mg and 1 pre-filled syringe solvent 1 mL, Cablivi®, Sanofi-Aventis Australia Pty Ltd.

1 Purpose of submission

1.1 The submission requested a Section 100 (Authority Required - telephone) listing for caplacizumab for the treatment of acquired thrombotic thrombocytopenic purpura (aTTP).

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus current standard of care (plasma exchange and immunosuppression).

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Adults with acquired thrombotic thrombocytopenic purpura (aTTP)
Intervention	Caplacizumab 10 mg daily (initial loading dose intravenous, all subsequent doses subcutaneous) in combination with plasma exchange and immunosuppression
Comparator	Placebo (standard of care: plasma exchange and immunosuppression)
Outcomes	Time to platelet normalisation, TTP-related death, TTP recurrence, TTP relapse, major thromboembolic events, refractory TTP, time to normalisation of organ damage markers
Clinical claim	In the treatment of aTTP, caplacizumab in combination with plasma exchange and immunosuppression has superior efficacy and inferior safety compared to standard of care alone

Source: Table 1.1, p.2 of the submission

2 Background

Registration status

2.1 Caplacizumab 10 mg was submitted under the Comparable Overseas Regulator Pathway A application process, and was registered on the ARTG on 5 February 2020 for the following indication: treatment of adults experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression. Caplacizumab has an orphan drug designation.

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Table 2: Essential elements of the requested listing: initial treatment

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Published (effective) Dispensed price for maximum quantity	Proprietary name and manufacturer
CAPLACIZUMAB 10 mg/mL, 1 x 10 mg powder for injection	4	4	0	$22,857.16 ($[redacted]) $22,904.55 ($[redacted])	Cablivi®, Sanofi-Aventis

Source: Table 1.7, p.19 of the submission

Table 3: Essential elements of the requested listing: initial treatment- extended initial treatment

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Published (effective) Dispensed price for maximum quantity	Proprietary name and manufacturer
CAPLACIZUMAB 10 mg/mL, 1 x 10 mg powder for injection	1	1	4	$5,714.29 ($[redacted]) $5,761.68 ($[redacted])	Cablivi®, Sanofi-Aventis

Source: Table 1.8, p.19 of the submission

Table 4: Essential elements of the requested listing: continuing treatment

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Published (effective) Dispensed price for maximum quantity	Proprietary name and manufacturer
CAPLACIZUMAB 10 mg/mL, 1 x 10 mg powder for injection	30	30	0	$171,428.70 ($[redacted]) $171,476.09 ($[redacted])	Cablivi®, Sanofi-Aventis

Source: Table 1.9, p.20 of the submission

Table 5: Essential elements of the requested listing: continuing treatment – extended continuing treatment

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Published (effective) Dispensed price for maximum quantity	Proprietary name and manufacturer
CAPLACIZUMAB 10 mg/mL, 1 x 10 mg powder for injection	7	7	0	$40,000.03 ($[redacted]) $40,047.42 ($[redacted])	Cablivi®, Sanofi-Aventis

Source: Table 1.10, p.20 of the submission

Table 6: Requested listing continuing treatment and extended continuing treatment

Category/Program	Section 100 HSD
Prescriber type	☐Dental ☒Medical practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity	Acute
Severity	Not applicable
Condition	Acquired thrombotic thrombocytopenic purpura
PBS indication	Acquired thrombotic thrombocytopenic purpura
Treatment phase	Continuing treatment
Restriction level/Method	☐Restricted benefit ☐Authority required – In writing ☒Authority required – Telephone ☐ Authority required – Emergency ☐ Authority required – Electronic ☐Streamlined

Category/Program	Section 100 HSD
Treatment criteria	~~Patient must be treated by a physician experienced in the treatment of patients with thrombotic microangiopathies~~ *Must be treated by, a nephrologist, or a haematologist, or, must be in consultation a nephrologist, or a haematologist*
Clinical criteria	~~Patient must have received treatment with caplacizumab under the Initial or Initial – Extended Initial Treatment of restrictions~~ *Patient must have been treated in hospital for confirmed aTTP with caplacizumab used in combination with plasma exchange and immunosuppression* **AND** *Patient must have had a normalised platelet count of greater than 150 x 10^9 platelets per litre for at least two consecutive days* *AND* *Patient must have ceased treatment with plasma exchange* *AND* Patient must not receive more than 30 days of treatment under this restriction
Population criteria	Patient must be 18 years of age or older
Prescriber instructions	The authority application must be made by telephone and must include: (1) A completed authority prescription form; and (2) A completed aTTP caplacizumab Authority Application for Continuing Treatment. *A confirmed diagnosis of aTTP is defined as ADAMTS13 activity less than 10% on a blood sample taken prior to plasma exchange or infusion*
Administrative Advice	*Special Pricing arrangements apply*
Category/Program	Section 100
Prescriber type	☐Dental ☒Medical practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity	Acute
Severity	Not applicable
Condition	Acquired thrombotic thrombocytopenic purpura
PBS indication	Acquired thrombotic thrombocytopenic purpura
Treatment phase	Extended continuing treatment
Restriction level/Method	☐Restricted benefit ☐Authority required – In writing ☒Authority required – Telephone ☐ Authority required – Emergency ☐ Authority required – Electronic ☐Streamlined
Treatment criteria	~~Patient must be treated by a physician experienced in the treatment of patients with thrombotic microangiopathies~~ *Must be treated by, a nephrologist, or a haematologist, or, must be in consultation a nephrologist, or a haematologist*
Clinical criteria	Patient must have received treatment with caplacizumab under the Continuing Treatment restriction **AND** Patient must have evidence of ongoing immunological disease, *defined as ADAMTS13 activity less than 10%* **AND** A patient may only receive treatment under this restriction a maximum of four times
Population criteria	Patient must be 18 years of age or older
Prescriber instructions	The authority application must be made by telephone and must include: (1) A completed authority prescription form; and (2) A completed aTTP caplacizumab Authority Application. The following documents must be kept on file:

Category/Program	Section 100 HSD
	(3) The result of ADAMTS13 activity and the date and time that the sample for the ADAMTS13 assay was collected.
Administrative advice	~~Ongoing immunological disease is defined as ADAMTS13 activity less than 10%~~ *Special Pricing arrangements apply*

3.2 The submission proposed a special pricing arrangement consisting of a [redacted]% discount on the published AEMP of $5,714.29 per vial (effective price $[redacted] per vial).

3.3 Caplacizumab is to be administered intravenously, once, prior to the commencement of plasma exchange, and subcutaneously once daily following daily plasma exchange. Two doses are therefore administered on day 1 of treatment. Treatment is to continue until 30 days after cessation of plasma exchange. The sponsor proposed providing the first 2 days (equivalent to 3 doses) of caplacizumab without charge, until diagnosis of aTTP is confirmed via ADAMTS13 activity test results. No mechanism was suggested for the provision of these initial doses in the submission. The ESC considered this did not impact the cost to the PBS as caplacizumab would only ever be initiated in the in-hospital setting, with in-patient use not suitable for funding on the PBS.

3.4 The requested listing was broadly consistent with the TGA indication for caplacizumab. Four restrictions were proposed:

- Initial treatment (4 vials): to provide caplacizumab during the plasma exchange treatment period following the proposed sponsor-reimbursed period (first 2 days) prior to confirmation of diagnosis;
- Initial treatment – extended initial treatment (up to 5 additional vials): to provide caplacizumab for patients requiring more than the average (5.5 days) duration of plasma exchange;
- Continuing treatment (30 vials): To provide treatment with caplacizumab for 30 days following the cessation of daily plasma exchange treatment;
- Extended continuing treatment (7 vials): For patients requiring extended treatment due to evidence of ongoing immunological disease following the standard 30-days of post-plasma exchange treatment.

3.5 Eligibility for extended treatment will be dependent on demonstration of ongoing immunological disease via ADAMTS13 activity testing, whereby evidence of ADAMTS13 activity less than 10% of normal indicates the requirement for extended treatment. The measurement of ADAMTS13 levels is a part of routine follow up in clinical practice, as ADAMTS13 deficiency can predict exacerbation or relapse. The cut off of <10% ADAMTS13 activity is broadly considered indicative of TTP, and is appropriate for monitoring disease activity. However, as caplacizumab does not target the underlying cause of the disease, the evaluation suggested it was unclear if ADAMTS13 deficiency is the most appropriate criterion for determining eligibility for treatment extension. The ESC considered ADAMTS13 activity was the most reliable and specific marker of disease activity. The ESC considered that using other markers

such as LDH or haptoglobin would lead to non-specific use of caplacizumab and also would miss early relapse resulting in potential for more severe relapse and increased morbidity and mortality. The ESC noted that while ADAMTS13 antibody testing is also specific to measuring disease activity, it is not clinically available for use.

3.6 The ESC considered it would be reasonable to expect monitoring of ADAMTS13 levels every 7 days in the initial 30-day post PEX period.

3.7 The four restrictions were designed based on the average duration of plasma exchange in the HERCULES trial. However, the duration of plasma exchange within the trial was highly variable (range: 1-35 days), and therefore the likely duration of treatment and suitability of the proposed restrictions is unclear. The ESC noted aTTP is a heterogeneous disease, with patients experiencing varied response times to treatment with PEX.

3.8 Caplacizumab will be initiated as an inpatient treatment during plasma exchange. The length of time a patient will remain hospitalised following cessation of daily plasma exchange varies from patient to patient, and is dependent on the patient's clinical status and the presence or absence of any ongoing signs or symptoms related to ischemic organ damage. As such, the entire period of co-administration alongside plasma exchange and a proportion of the 30 day post-plasma exchange caplacizumab treatment will occur whilst the patient remains in hospital, with the remainder being self-administered in the outpatient setting, with the relative length of each period varying from patient to patient. The ESC recalled that public hospital inpatient treatment is not subsidised by the PBS. Therefore, the ESC noted that the inpatient component of funding in public hospitals will require joint funding between the Commonwealth, states and territories under the usual National Health Reform Agreement (NHRA) arrangements, with only outpatient treatment to be subsidised under the PBS. The total duration of hospitalisation was variable in the HERCULES trial (median of 9 days, range: 2-37 days). The ESC advised that the appropriate number of vials dispensed on the PBS needs to take into consideration that a significant component of the treatment may occur during inpatient stay.

3.9 The proposed restriction requests that following the completion of plasma exchange, patients continue treatment with caplacizumab for an additional 30 days. It is therefore proposed that, for the continuing treatment restriction, patients will be dispensed with 30 vials on day one of the continuing treatment, with the intention that the hospital pharmacy will supply one vial daily whilst the patient remains in hospital, with any remaining vials supplied to the patient on discharge. This quantity may not be appropriate given the proposed price of caplacizumab. The ESC advised that some patients will be discharged with significantly less than 30 days of post-PEX treatment with caplacizumab remaining. Therefore the ESC considered it was appropriate for the continuing treatment restriction be revised to provide patients with a reduced maximum quantity and increased number of repeats (up to 30 days' worth of treatment).

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 Thrombotic thrombocytopenic purpura (TTP) is a well-defined entity of a heterogeneous group of disorders, the thrombotic microangiopathies. Acquired thrombotic thrombocytopenic purpura (aTTP) is a life-threatening, autoimmune blood clotting disorder manifested by microvascular occlusions and consequent thrombocytopenia, haemolytic anaemia with red cell fragmentation, and organ ischemia due to disturbed microcirculation. It is a rare disease with an incidence of 1.2 to 11 cases per million per year. The incidence in children (<18 years) is low, about 3% of that in adults. aTTP generally occurs in adulthood and is more common in women (2:1 vs men) and people of African descent. The median age at diagnosis is approximately 40 years. A trigger, including physical stress (such as surgery), infections, drug intake or a pregnancy may precipitate the disease.

4.2 aTTP is characterised by the production of inhibitory autoantibodies to the metalloproteinase ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, 13), which is responsible for cleaving ultra-large von Willebrand Factor multimers into their individual subunits. Decreased ADAMTS13 activity leads to an accumulation of von Willebrand Factor multimers which bind to platelets and induce adhesion. The consumption of platelets into these microthrombi causes severe thrombocytopenia, tissue ischemia and organ dysfunction, commonly involving the brain, heart, and kidneys, and resulting in acute thromboembolic events such as stroke, myocardial infarction, and venous thrombosis, and early death. Left untreated, aTTP is progressive, with irreversible renal failure, neurological deterioration and 90% mortality. With prompt initiation of empirical therapeutic plasma exchange, the average survival rate from a first episode of TTP is 80% to 90%.

4.3 TTP is characterised by thrombotic microangiopathy, or the formation of blood clots in small blood vessels throughout the body, which can lead to microangiopathic haemolytic anaemia and thrombocytopenia. This characteristic is shared by two related syndromes, haemolytic-uremic syndrome (HUS) and atypical haemolytic uremic syndrome (aHUS). Consequently, differential diagnosis is essential. Unlike HUS and aHUS, aTTP is known to be caused by an acquired defect in the ADAMTS13 protein, so a lab test showing ≤10% of normal ADAMTS13 levels is indicative of aTTP. ADAMTS13 activity testing is an important adjunct for the clinical diagnosis, but this testing cannot be used in isolation, nor should therapy be delayed when appropriate while waiting for results of this testing.

4.4 The disease course is unpredictable. The key clinical symptoms of aTTP are, as for all types of thrombotic microangiopathy, symptoms of Coombs negative haemolysis with red cell fragmentation, consumption thrombocytopenia and signs of disturbed microcirculation. The symptoms of organ dysfunction are often nonspecific and very

variable, possibly involving the brain, kidneys, heart, lungs, pancreas, or gut. Initially, a presumptive diagnosis of aTTP is made based on clinical features and initial laboratory testing, with treatment initiated whilst awaiting ADAMTS13 activity testing results. Concurrently with initiation of therapy, individuals with a presumptive diagnosis of aTTP should have ongoing consideration of other possible causes of their symptoms, including other primary thrombotic microangiopathies and other systemic conditions.

4.5 Most patients (85 to 90 percent) with aTTP ultimately recover following treatment with plasma exchange, glucocorticoids, and rituximab. Relapses have been reported in 30-40% of patients. Whilst most patients with aTTP do not experience a relapse, a relapse may be triggered by illness, surgery, major trauma, or pregnancy. Patients are monitored over time for the purpose of detecting relapse. Relapses are generally identified because the patient develops symptoms similar to their initial episode such as bruising, dark urine, neurologic symptoms, or unexplained severe fatigue.

4.6 The ESC advised that patients are monitored for recurrence after platelet normalisation by measuring ADAMTS13 levels. If levels drop below 10% and a patient is clinically well, they may be treated with rituximab alone, or used with an immunosuppressant. However in certain circumstances, PEX + corticosteroids will have to be reinstated in order to effectively treat an exacerbation.

4.7 Long-term follow-up observations have documented increased risks for multiple health problems in individuals who have recovered from an episode of acquired TTP. These risks include minor cognitive impairment, major depression, hypertension, abnormal kidney function, and development of systemic lupus erythematosus.

4.8 Targeting a high risk population may be more likely to derive a higher absolute benefit from treatment (for example, refractory patients). The ESC noted both clinical trials presented in the submission, TITAN and HERCULES, did not use caplacizumab as rescue therapy (in refractory patients). Therefore the ESC considered it was difficult to assess whether a higher absolute benefit of treatment would be derived from limiting treatment to use in later lines of therapy.

4.9 The ESC noted the pre-sub-committee response (PSCR) highlighted the International Society of Thrombosis and Haemostasis (ISTH) Clinical Guidelines, which were available online in their final draft stage, placed caplacizumab treatment in the early phase of an acute event of aTTP. All other guidelines were published before availability of the pivotal studies and therefore do not discuss the use of caplacizumab in the treatment of aTTP.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 Current standard of care for patients with aTTP is plasma exchange plus immunosuppression with corticosteroids ± rituximab. Caplacizumab is to be used as an add-on therapy to plasma exchange plus immunosuppression. Therefore, the submission nominated standard of care as the main comparator. This was appropriate. Rituximab is not currently PBS listed for the treatment of aTTP.

5.2 The ESC advised rituximab is very commonly used as off-label treatment in aTTP. The ESC further stated that rituximab is not usually used as a first line treatment in aTTP but rather, is used post commencement of PEX + corticosteroids in patients that appear to be refractory to treatment. As rituximab is not PBS listed for the treatment of aTTP, access to the treatment is dependent on the funding and accessibility arrangements present at each hospital. This leads to variation in time to treatment with rituximab amongst refractory patients (24 hours post PEX- one week post PEX) as well as uncertainty as to the extent of its use in the Australian setting.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor Hearing

6.1 There was no hearing for this item

Consumer Comments

5.3 No consumer comments were received for this item.

Clinical trials

6.2 The submission was based on two head-to-head trials, both of which compared caplacizumab in combination with standard of care (comprising plasma exchange and immunosuppression), with standard of care alone, in patients with symptoms of aTTP who required treatment with plasma exchange: TITAN and HERCULES.

6.3 The TITAN study was a Phase II trial comparing the effectiveness of the addition of caplacizumab to plasma exchange and immunosuppression, with caplacizumab administered for an additional 30 days after finishing plasma exchange. The HERCULES trial was a Phase III trial, which permitted up to an additional 4 weeks of caplacizumab following the first 30 days of treatment post-plasma exchange.

6.4 Details of the trials presented in the submission are provided in the table below.

Table 7: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
HERCULES	A Phase III Double-Blind, Randomized, Parallel Group, Multicenter Placebo-Controlled Trial to Study the Efficacy and Safety of Caplacizumab in Patients with Acquired Thrombotic Thrombocytopenic Purpura	June 2018
	Scully M, Cataland SR, Peyvandi F, Coppo P, Knol P, Kremer Hovinga JA, Metjian A, De La Rubia J, Pavenski K, Callewaert F, Biswas D, De Winter H and Zeldin RK. Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura.	*NEJM* 2019; 380(4): 335-346
	Yang Z, McCaw ZR and Yin G. Caplacizumab for acquired thrombotic thrombocytopenic purpura.	*NEJM* 2019; 380(18): E32
	Knoebl P, Cataland S, Peyvandi F, Coppo P, Scully M, Kremer Hovinga JA, Metjian A, de la Rubia J, Pavenski K, Minkue Mi Edou J, De Winter H and Callewaert F. Efficacy and safety of open-label caplacizumab in patients with exacerbations of acquired thrombotic thrombocytopenic purpura in the HERCULES study.	*J Thromb Haemost* 2019; e14679
TITAN	A Phase II, single-blind, randomised, placebo-controlled trial to study the efficacy and safety of anti-von Willebrand factor Nanobody administered as adjunctive treatment to patients with acquired thrombotic thrombocytopenic purpura	May 2015
	Peyvandi F, Scully M, Kremer Hovinga JA, Cataland S, Knobl P, Wu H, Artoni A, Westwood JP, Taleghani MM, Jilma B, Callewaert F, Ulrichts H, Duby C and Tersago D. Caplacizumab for acquired thrombotic thrombocytopenic purpura	*NEJM* 2016; 374(6): 511-522
	Abdelghany MT and Baggett MV. Caplacizumab for acquired thrombotic thrombocytopenic purpura.	*NEJM* 2016; 374(25): 2497
	Peyvandi F, Scully M, Kremer Hovinga JA, Knöbl P, Cataland S, De Beuf K, Callewaert F, De Winter H and Zeldin RK. Caplacizumab reduces the frequency of major thromboembolic events, exacerbations and death in patients with acquired thrombotic thrombocytopenic purpura	*J Thromb Haemost* 2017; 15(7): 1448-1452

Source: Table 2.2.1, pp.30-32 of the submission

6.5 The key features of the trials are summarised in the table below.

Table 8: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Caplacizumab plus standard of care versus standard of care alone (plasma exchange + immunosuppression)						
HERCULES	145	R, DB, MC, PC Variable duration	Unclear	Adults with an acute episode of aTTP[a]	Platelet count normalisation; composite of TTP related death, recurrence of TTP, or at least one major thromboembolic event	Thromboembolic events, TTP-related death, treatment-related serious bleeding events, plasma exchange complications, duration of hospitalisation, duration of plasma exchange
TITAN	75	R, SB, MC, PC Variable duration	High	Adults with an acute episode of aTTP[b]	Platelet count normalisation; composite of TTP related death, recurrence of TTP, or at least one major thromboembolic event	TTP-related death

Source: Section 2 of the submission

Abbreviations: DB, double blind; MC, multi-centre; R, randomised; SB, single blind; TTP, thrombotic thrombocytopenic purpura

[a] Participants were eligible if they had TTP that was diagnosed on the basis of clinical presentation (the presence of both thrombocytopenia and microangiopathic haemolytic anaemia with schistocytes seen on blood smear) and if they had received exactly one plasma-exchange treatment. Severe ADAMTS13 deficiency was not an eligibility criterion.

[b] Adults with an acute episode of acquired TTP were eligible for the study if they had a platelet count of less than 100,000 per cubic millimetre, without active bleeding, and required plasma exchange.

6.6 Due to recruitment challenges, the TITAN study was prematurely terminated to assess whether to continue clinical development. The actual number of patients randomised was 75, as opposed to the target of 110. There were also a number of protocol amendments, issues with the local and central laboratories resulting in uncertainties regarding the integrity and identity for an unknown number of the samples, missing data, the extent of which was unclear, and a number of important analyses conducted post-hoc, with several secondary outcomes therefore associated with varying levels of uncertainty. Therefore, the TITAN study was considered to have a high risk of bias. The results of this study should be considered proof-of-concept only, and not relied upon for determination of efficacy.

6.7 In the HERCULES trial recurrence was measured as part of the composite outcome including death, recurrence or major thromboembolic event. Recurrence was defined as recurrent thrombocytopenia after initial recovery of platelet count (per primary outcome) requiring re-initiation of daily PEX during the overall study period (including 4-week FU period). Exacerbation was defined as recurrence of TTP during the first 30-day post-daily PEX period; Relapse was defined as recurrence of TTP after the 30-day post-daily PEX period.

6.8 The HERCULES trial allowed patients in either treatment arm to cross over to open label caplacizumab in case of exacerbation, defined as recurrent thrombocytopenia after initial recovery of platelet count (daily plasma exchange must have been stopped for at least one day), requiring re-initiation of daily plasma exchange, occurring during the first 30-days post-daily plasma exchange period.

6.9 No correction for crossover was applied in the analysis of results. Therefore, results for the overall treatment period (as opposed to the double blind period), which

contains open label treatment, are contaminated by crossover to active treatment. It is unclear how results from the overall treatment period should be construed; results from the overall treatment period should be interpreted with caution. There were also a number of post-randomisation differences between treatment arms, including different discontinuation rates, higher rituximab use in the placebo arm versus higher rates of other immunosuppressive therapies in the caplacizumab arm, and a higher rate of treatment extensions in the caplacizumab arm. Further, there were a number of differences in disease characteristics at baseline (initial vs. recurrent episode of disease; history of thromboembolic events) between treatment arms. Because of these issues, the overall risk of bias in the HERCULES trial was judged to be unclear. The ESC considered the increased use of rituximab in the placebo arm would be expected if patients in this treatment arm were not responding as well as the caplacizumab arm; rituximab is commonly used as a rescue medication in this situation.

6.10 The TITAN and HERCULES studies did not include longer-term treatment or follow up to assess the impact of treatment with caplacizumab on the long-term sequelae of aTTP. Although some retreatment was allowed for exacerbations, there is also limited data available on the efficacy and safety of retreatment with caplacizumab. Patients who completed the 28 day follow-up visit in HERCULES were able to join an open-label post-HERCULES study, which will assess effectiveness of retreatment. If a patient experienced recurrence of TTP during this follow up study, open-label caplacizumab was commenced. The follow-up study was ongoing at the time of the submission, with an estimated completion date of October 2020. The ESC noted that many of the long-term sequelae of aTTP occur as a result of the initial aTTP event, due to the organ damage caused by the microangiopathic changes, resulting in strokes, acute myocardial infarctions, chronic renal impairment etc. Therefore the ESC considered it would be reasonable to assume that the better and faster you control microangiopathic events initially, the less long-term sequelae would be experienced; however the ESC noted this is not well documented and the trials were limited by small patient numbers and lack of long-term follow-up data. The ESC advised this was particularly problematic for the economic modelling.

6.11 Patients in the HERCULES trial were randomised following their first dose of plasma exchange. Once the platelet count was ≥ $150x10^9$/L, daily plasma exchange was to continue for at least two further days. Tapering of plasma exchange after platelet count normalisation, defined as reducing its frequency to less than once per day, was strongly discouraged in the protocol. All patients enrolled in the HERCULES trial received corticosteroids, either intravenous or orally during the daily plasma exchange period, and continued for the first week after the end of daily plasma exchange. Other immunosuppressive treatments including rituximab were permitted in HERCULES per standard site practice, but had to be considered in light of protocol required corticosteroid treatment. The treatment protocol for standard of care in HERCULES

may not reflect current standard of care in clinical practice, including use of plasma exchange tapering, duration of corticosteroids, and use of rituximab. It is possible this led to protocol driven events occurring in HERCULES; given that duration of plasma exchange was an outcome, and tapering of plasma exchange was not allowed, the initial duration of plasma exchange may be reduced compared with clinical practice. The ESC noted the PSCR suggested the HERCULES trial was applicable to proposed PBS population, with the protocol of stopping PEX two days after platelet normalisation being the same as Australian clinical practice, and the mean duration of PEX in the trial (10.4 days) being similar to that reported in the Australian clinician survey presented in the submission (11 days). The ESC considered that given this is a rare disease and treatment is delivered by haematologists who are specialised in the care of TTP as well as experienced in clinical trials, it is unlikely that PEX would be used longer than required in clinical practice.

6.12 There were a high number of exacerbations (38% during the first 30 days post-plasma exchange) in the placebo arm of the HERCULES trial. Further, although rituximab is increasingly being recommended as part of the initial treatment for aTTP alongside plasma exchange in a number of published treatment guidelines, based on evidence from a number of studies that it reduces the risks of exacerbation and relapse, its use was discouraged in HERCULES. However, it is likely to be used in the majority of patients in current practice. In the HERCULES trial, only 16.7% of patients in the caplacizumab arm and 28.8% of patients in the placebo arm received rituximab at initiation during the double blind treatment period. The ESC advised that rituximab is standard of care for this indication in most Australian centres for patients who fail to initially respond to PEX. However, it is not funded by the PBS and is currently supplied through hospital based funding. Use of caplacizumab will likely reduce use of rituximab but this will not have an effect on the PBS budget.

Comparative effectiveness

6.13 The results for the primary outcome, time to confirmed platelet count response, in both TITAN and HERCULES are summarised in Table 9.

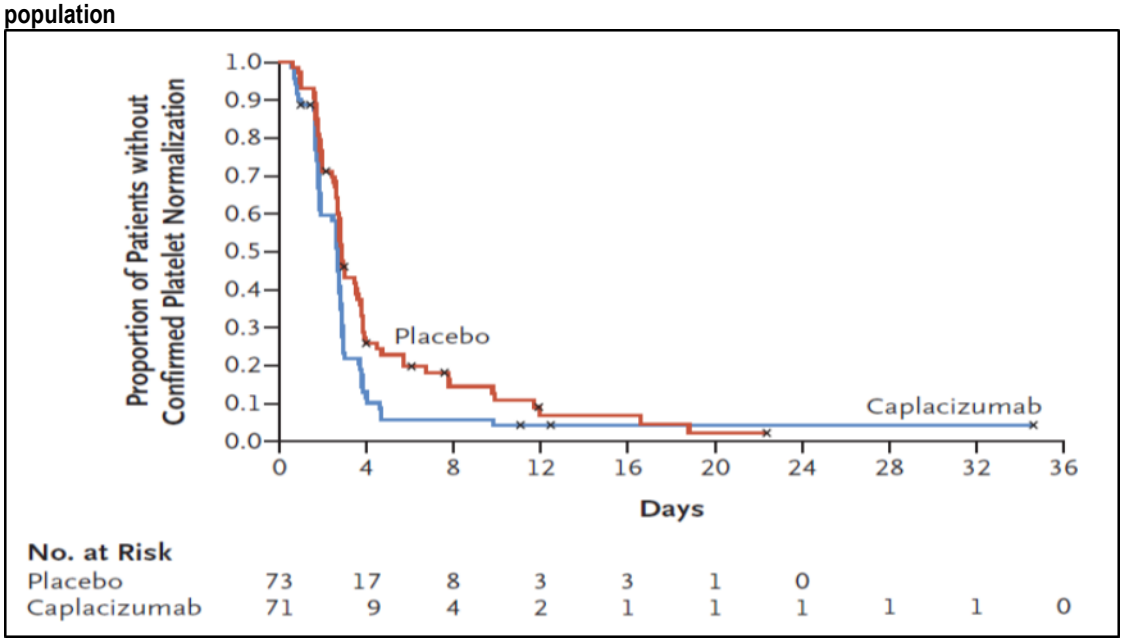
Table 9: Time to confirmed platelet count response: (m) ITT population (double blind treatment period)

	Caplacizumab Number achieving response, n/N (%)	**Placebo Number achieving response, n/N (%)**	**Hazard ratio (95% CI)**
HERCULES	66/71 (93.0%)	66/73 (90.4%)	1.55 (1.10, 2.20)
TITAN	31/36 (86.1%)	28/39 (71.8%)	2.20 (1.28, 3.78)
	Median days to response (95% CI)	**Median days to response (95% CI)**	**Difference caplacizumab versus placebo**
HERCULES	2.69 (1.89, 2.83)	2.88 (2.68, 3.56)	-0.19
TITAN	3.00 (2.74, 3.88)	4.92 (3.21, 6.59)	-1.92

Source: Table 2.5.1; Table 2.5.2, p.62 of the submission

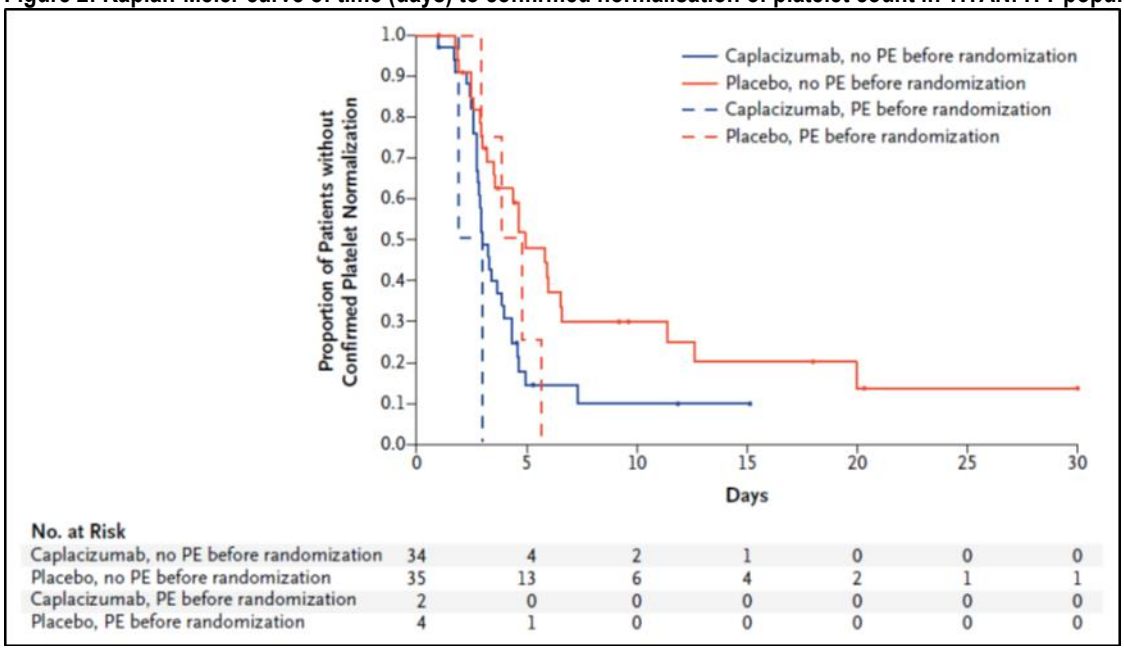
6.14 Figure 1 and 2, below, show time to confirmed platelet normalisation (days) in HERCULES and TITAN respectively.

Figure 1: Kaplan-Meier curve of time (days) to confirmed normalisation of platelet count in HERCULES: mITT population



Source: Figure 2.5.2, p.63 of the submission
Abbreviations: mITT, modified intention to treat
Notes (from submission): Response defined as initial platelet count ≥ 150x109/L with subsequent stop of daily plasma exchange within five days. Symbols indicate censored data. Patients without response by 45 days after start of study drug were censored at 45 days.

Figure 2: Kaplan-Meier curve of time (days) to confirmed normalisation of platelet count in TITAN: ITT population



Source: Figure 2.5.1, p.63 of the submission
Abbreviations: ITT, intention to treat; LDH, lactate dehydrogenase; PE, plasma exchange; ULN, upper limit of normal
Notes: Response defined as recovery of platelet count ≥ $150x10^9$/L which was confirmed 48 hours after the initial reporting of platelet recovery by a de novo measure of platelet count ≥ $150x10^9$/L and LDH ≤2 x ULN.
Symbols indicate censored data. Patients without response by 30 days after start of study drug were censored at 30 days

6.15 Caplacizumab statistically significantly reduced the time to confirmed platelet count response compared with placebo in HERCULES (HR of 1.55; 95% CI: 1.095, 2.195). The difference in median time to achieve response between treatment arms was not large, being 0.19 days (2.69 vs 2.88), or 1.55 days in the 75th percentile (2.95 vs 4.50). The confidence intervals for the hazard ratio were wide suggesting that the study had low power to detect an association with strong statistical support, and the survival curves are initially close, diverge and reconverge, and cross between day 16 and day 20. It is therefore unclear whether the proportional hazards assumption was met. The submission stated that despite the curves crossing at approximately day 17 the proportional hazards assumption was not violated (tested graphically by empirical score process and numerically by supremum testing; results not provided).

6.16 The ESC noted that platelet normalisation is the marker by which response to treatment is assessed. The ESC considered that while a reduction in the time to platelet normalisation is clinically significant if it results in a reduction in the number of days on PEX (thereby reducing potential complications associated with PEX), the median reduction of 0.19 days (or 4.56 hours) seen in the caplacizumab arm of the HERCULES trial is not clinically meaningful, given that PEX is administered daily.

6.17 The result for the composite secondary outcome of TTP-related death, recurrence of TTP or major thromboembolic event are summarised in Table 10.

Table 10: Composite of TTP-related death, recurrence of TTP or major thromboembolic event in HERCULES (mITT; double blind treatment period) and TITAN (safety population)

	Caplacizumab, n/N (%)	Placebo, n/N (%)
HERCULES		
Composite endpoint	9/71 (12.7)	36/73 (49.3)
TTP-related mortality during DB treatment period	0/71	3/73 (4.1)
Major thromboembolic event during DB treatment period	6/71 (8.5)	6/73 (8.2)
Recurrence during treatment DB period: exacerbations[a]	3/71 (4.2)	28/73 (38.4)
Recurrence of TTP during the 1-month Follow-up Period (including open-label treatment): relapses	6/71 (8.5%)[b]	0/73 (0%)
Recurrence of TTP during one year Follow-up Period (including open-label treatment): relapses	NA	NA
Recurrence of TTP at any time during Overall Study Period until 1-month follow-up (including open-label treatment)	9/71 (12.7%)	28/73 (38.4%)
TITAN		
Composite endpoint	4/35 (11.4)	16/37 (43.2)
TTP-related mortality during study	0/35	2/37 (5.4)
Major thromboembolic event during treatment period	1/35 (2.9)	6/37 (16.2)
Recurrence during treatment period	3/35 (8.6)	11/37 (29.7)
Recurrence of TTP during the 1-month Follow-up Period: relapses	8/36 (22%)	0/39 (0%)
Recurrence of TTP during one year Follow-up Period: relapses	11/36 (30.6%)	3/39 (7.7%)
Recurrence of TTP at any time during Overall Study Period until 1-month follow-up	10/36 (27.8%)	11/39 (28.2%)

Source: Table 2.5.3, Table 2.5.4, & Table 2.5.5 pp.65 and 66 of the submission

[a] The DB Treatment Period of HERCULES included the PEX period, 30 days post-PEX period and treatment extension period if required. However, all recurrences during the DB Treatment Period of HERCULES occurred within 30 days of stopping PEX ((Scully 2019 p339; HERCULES CSR p130) and thus meet the definition of exacerbation. The SB Treatment Period of TITAN only extended for 30 days after stopping PEX and thus all recurrences within this period also meet the definition of exacerbation.

[b] The HERCULES CSR reports 6 out of 66 patients in the caplacizumab group (9.1%) experienced recurrence during follow-up whereas Scully 2019 reported 6 out of 72 (8%) based on the ITT population. In the table above, the mITT population is used as it is less conservative than the ITT population.

6.18 Treatment with caplacizumab was associated with a statistically significantly improvement in the composite endpoint of TTP-related mortality, recurrence, or major thromboembolic event compared with placebo. This difference was primarily driven by disease recurrence. Given the higher proportion of patients in the placebo arm with recurrent disease at baseline, the significance of this result is unclear. Further, there are protocol-driven differences in on-trial treatment that may have reduced the period of time spent on plasma exchange compared with current clinical practice, thereby increasing the risk of disease recurrence, particularly in the placebo group.

6.19 The result for TTP-related mortality in the TITAN and HERCULES trials is summarised in Table 11.

Table 11: Mortality across TITAN and HERCULES trials

	TITAN (ITT population)		HERCULES (mITT population)	
	Caplacizumab (N=36)	Placebo (N=39)	Caplacizumab (N=71)	Placebo (N=73)
Daily PEX period	0	0	0	3 (4.1%)
Overall Treatment Period	0	0	0	3 (4.1%)
During 1-month follow-up	0	2 (5.1%)	1 (1.4%)	0
Total: Overall Study Period	0	2 (5.1%)	1 (1.4%)	3 (4.1%)

Source: Table 2.5.6, p.68 of the submission
Abbreviations: ITT, intention to treat; mITT, modified intention to treat; PEX, plasma exchange

6.20 The ESC agreed with the evaluation that although there is a numerical trend towards a reduction in mortality associated with treatment with caplacizumab, this is based on very small numbers of events and cannot be used to draw a conclusion about efficacy.

6.21 Major thromboembolic events are summarised in Table 12.

Table 12: Major thromboembolic events across the TITAN and HERCULES trials

	Caplacizumab	Placebo
HERCULES (mITT)		
At least one event	6/71 (8.5%)	6/73 (8.2%)
Myocardial infarction	1/71 (1.4%)	1/73 (1.4%)
Pulmonary embolism	1/71 (1.4%)	0
Deep venous thrombosis (spontaneous)	0	1/73 (1.4%)
Deep venous thrombosis (catheter associated)	3/71 (4.2%)	2/73 (2.7%)
Cerebrovascular accident	2/71 (2.8%)	3/73 (4.1%)
TITAN (Safety population)		
At least one event	1/35 (2.9%)	6/37 (16.2%)
Acute myocardial infarction	0	2/37 (5.4%)
Pulmonary embolism	1/35 (2.9%)	1/37 (2.7%)
Deep vein thrombosis	0	1/37 (2.7%)
Venous thrombosis	0	1/37 (2.7%)
Ischemic stroke	0	1/37 (2.7%)
Haemorrhagic stroke	0	1/37 (2.7%)

Source: Table 2.5.7, p.69 of the submission
Abbreviations: DB, double blind; mITT, modified intention to treat; SB, single blind
The data in the table are number of patients with at least one event of interest and corresponding percentage

6.22 There were no appreciable differences between treatment arms in the overall numbers of events in the HERCULES trial. Although there is a numerical trend towards a reduction in some individual events associated with treatment with caplacizumab (stroke), this is offset by an increase in other events associated with caplacizumab (deep vein thrombosis, pulmonary embolism). These results are based on very small numbers of events and are unlikely to be clinically meaningful. In the TITAN trial, there was a greater risk of thromboembolic events in the placebo treatment arm.

6.23 The average number of days of plasma exchange in the HERCULES and TITAN trials are summarised in Table 13.

Table 13: Use of plasma exchange across TITAN and HERCULES

	n	Caplacizumab	n	Placebo
HERCULES (mITT)				
Number of days with at least one PEX session (initial treatment period)				
Mean (SD)	71	5.5 (*4.04*)	73	6.5 (*3.84*)
Median (range)	71	5.0 (1, 35)	73	5.0 (3, 22)
Number of days with at least one PEX session (open label period)				
Mean (SD)	2	7.5 (*12.64*)	26	6.9 (*7.35*)
Median (range)	2	7. 5 (6, 9)	26	6.0 (2, 26)
Number of days with at least one PEX session (overall treatment period)[b]				
Mean (SD)	71	5.8 (*12.72*)	73	9.4 (*6.92*)
Median (range)	71	5.0 (1, 35)	73	7.0 (3, 46)
TITAN (Safety population)				
Number of days with at least one PEX session (initial treatment period)				
Mean (SD)	35	5.9 (2.43)	37	7.9 (6.43)
Median (range)	35	5.0 (3, 15)	37	6.0 (2, 35)
Number of PEX sessions[a] (initial treatment period)				
Mean (SD)	35	6.7 (3.69)	37	8.4 (6.74)
Median (range)	35	6.0 (3, 22)	37	6.0 (3, 36)
Number of days with at least one PEX session (overall treatment period)[b]				
Mean (SD)	35	7.7 (4.7)	37	11.7 (8.5)
Median (range)	35	6 (3, 21)	37	8 (2, 43)

Source: Table 2.5.12, p.72-3 of the submission

Abbreviations: ITT, intention to treat; mITT, modified intention to treat; NR, not reported; OL, open label; PEX, plasma exchange; SD, standard deviation; SE, standard error

Values in italics were calculated during the evaluation

[a] PEX was able to be administered more than once per day in TITAN, but was daily in HERCULES.

[b] Includes PEX after exacerbation in TITAN and during open-label caplacizumab period (due to exacerbation or relapse) in HERCULES

6.24 During the double blind treatment period of the HERCULES trial, there was a mean one day reduction in plasma exchange for caplacizumab versus placebo. There was no difference in the median days of plasma exchange. The first session of plasma exchange in HERCULES occurred pre-randomisation and was not included in the calculation of mean and median duration. A similar difference between treatment arms was observed in terms of volume of plasma exchange. The difference between treatment arms for the overall study period, which includes significant crossover from the placebo arm to open label caplacizumab, was more pronounced (mean 5.8 vs. 9.4 days), however due to the crossover this difference is difficult to interpret. This difference may also be protocol driven, since based on the evidence presented in the submission the risk of disease recurrence, and therefore additional plasma exchange and crossover to caplacizumab, was high in the placebo arm.

6.25 Similarly, in the TITAN trial, treatment with caplacizumab was associated with a reduction in the number of days and volume of plasma exchange compared with placebo.

6.26 In HERCULES, the mean length of stay in hospital (which included time in ICU) during the initial treatment period, overall treatment period, and overall study period was shorter in the caplacizumab group compared with the placebo group (5.5 days vs 6.8 days*)*. Median days hospital stay for that period was equal at 5 days. Overall, 54 patients were admitted to ICU during the HERCULES study, 28 randomised to caplacizumab (39.4%) and 27 randomised to placebo (37.0%). As noted above, there was significant crossover to open label caplacizumab, and the protocol driven outcomes lead to a higher risk of recurrence in the placebo arm leading to additional plasma exchange and longer hospital stays.

6.27 No quality of life data were captured in the HERCULES and TITAN trials.

6.28 The submission presented a number of subgroups, however did not rely on these for their clinical claim. Subgroup analysis by previous experience of a TTP episode showed a similar time to confirmed platelet count, with a trend towards a lower incidence of secondary outcomes (composite and components of TTP-related death, recurrence of TTP or major thromboembolic event) in patients experiencing a recurrent episode versus an initial episode. Analyses by baseline disease severity were broadly consistent across subgroups. Subgroup results for immunosuppressive therapy at baseline suggest similar outcomes irrespective of the type of initial immunosuppression used. However, these results should be interpreted with caution as they are based on a small numbers of patients, whose treatment was unlikely to be representative of current standard of care.

Comparative harms

6.29 A summary of adverse events in the TITAN and HERCULES studies is provided in Table 14.

Table 14: Adverse events in TITAN and HERCULES during overall study period: safety population

	TITAN		HERCULES		
	SB caplacizumab (N=35)	SB placebo (N=37)	DB caplacizumab (N=71)	DB placebo (N=73)	OL caplacizumab (N=28)
At least one treatment emergent adverse event	34 (97.1%)	37 (100%)	69 (97.2%)	71 (97.3%)	25 (89.3%)
At least one serious adverse event	20 (57.1%)	19 (51.4%)	28 (39.4%)	39 (53.4%)	7 (25.0%)
At least one serious adverse event excl. TTP	13 (37%)	12 (32%)	23 (32.4%)	12 (16.4%)	NR
Adverse event leading to death	0	2 (5.4%)	1 (1.4%)	3 (4.1%)	0
Adverse event leading to discontinuation of study drug	4 (11.4%)	2 (5.4%)	5 (7.0%)	9 (12.3%)	1 (3.6%)
At least one study drug related treatment emergent adverse event	20 (57.1%)	5 (13.5%)	41 (57.7%)	32 (43.8%)	20 (71.4%)
At least one bleeding related treatment emergent adverse event[a]	19 (54.3%)	14 (37.8%)	49 (69.0%)	49 (67.1%)	22 (78.6%)
At least one bleeding event (case report form documented event with increased bleeding tendency)	NR	NR	47 (66.2%)	36 (49.3%)	21 (75.0)

Source: Table 2.5.14, p.76 of the submission; Table 36, p.174; Table 37, p.175 of the HERCULES trial report.

Abbreviations: DB, double blind; SB, single blind; OL, open label; NR, not reported; PEX, plasma exchange; TTP, thrombotic thrombocytopenic purpura

Notes: Data are number (percentage) of patients with at least one event during the Overall Study Period which includes treatment-free follow-up.

[a] definition not reported in TITAN; defined by standardised MedDRA query for HERCULES (includes TTP).

6.30 In HERCULES more patients in the double blind placebo group experienced at least one serious adverse event (53.4%) compared with the double blind caplacizumab group (39.4%), while the proportions were similar in TITAN (caplacizumab 57.1% versus placebo 51.4%). In the HERCULES trial, this difference was primarily due to adverse events related to TTP, including exacerbation, relapse, recurrence, or worsening of TTP. When TTP events were excluded, the rates of serious adverse events were higher in the double blind caplacizumab group (32.4%) compared with the double blind placebo group (16.4%).

6.31 In the HERCULES trial, 3 patients in the double blind placebo group and 1 in the double blind caplacizumab group died during the trial. The caplacizumab treated patient died of cerebral ischemia 6 days after their last dose of study drug, which was not considered related to therapy. Two patients died in the TITAN study, both had been randomised to placebo.

6.32 Adverse events leading to discontinuation of study drug was higher in the caplacizumab group of TITAN versus placebo (11.4% vs 5.4%) but lower in the caplacizumab group of HERCULES versus placebo (7.0% vs 12.3%).

6.33 Bleeding-related adverse events were specified in the protocol as adverse events of special interest. In the HERCULES trial, bleeding-related events were reported for 49 patients (69.0%) in the double blind caplacizumab group, 49 patients (67.1%) in the double blind placebo group, and 22 patients (78.6%) in the open label caplacizumab

group during the overall study period. Due to the definition of these events, which included TTP-related bleeding, bleeding treatment-emergent adverse events were also collected based on an Investigator assessment of the event, i.e., investigators indicated whether they considered the adverse event an event indicative of an increased bleeding tendency. When these data are considered, bleeding adverse events were reported for 47 patients (66.2%) in the double blind caplacizumab group, 36 patients (49.3%) in the double blind placebo group, and 21 (75%) of patients in the open label caplacizumab group. Two patients in the HERCULES trial experienced serious bleeding related treatment emergent adverse events which were considered at least potentially related to caplacizumab: one case each of subarachnoid haemorrhage and uterine bleeding.

6.34 Treatment-related serious bleeding events in the HERCULES trial are summarised in Table 15.

Table 15: Treatment-related serious bleeding events: HERCULES

	Placebo (N=73)	Caplacizumab (N=71)	OL caplacizumab (N=28)	Total caplacizumab (DB + OL)
At least one treatment-related serious bleeding adverse event	3 (4.1)	8 (11.3)	1 (3.6)	9 (9.3)
Gastrointestinal disorders Gingival bleeding Upper gastrointestinal haemorrhage Haematemesis	0 0 0 0	3 (4.2) 1 (1.4) 1 (1.4) 1 (1.4)	1 (3.6) 0 1 (3.6) 0	4 (4.1) 1 (1.0) 2 (2.1) 1 (1.0)
Nervous system disorders Haemorrhagic transformation stroke	1 (1.40) 1 (1.4)	0 0	0 0	0 0
Respiratory, thoracic, and mediastinal disorders	0	4 (5.6)	0	4 (4.1)
Epistaxis	0	4 (5.6)	0	4 (4.1)
Bloody and lymphatic system disorders	2 (2.7)	0	0	0
Thrombotic thrombocytopenic purpura	2 (2.7)	0	0	0

Source: Table 14.3.1.12, HERCULES CSR

6.35 In the HERCULES trial, the most frequently reported bleeding events for double blind caplacizumab were gingival bleeding and epistaxis, and the most frequently reported bleeding events for double blind placebo were TTP and contusion. The majority of bleeding events were of mild to moderate severity. Severe bleeding events were reported in 7 patients in the double blind caplacizumab group (9.9%) and 12 in the double blind placebo group (16.4%), however most of which were TTP-related (caplacizumab: 4 patients vs placebo: 11 patients). In the double blind caplacizumab group, three severe bleeding events, apart from TTP, were reported: one each of epistaxis, gingival bleeding, and upper gastrointestinal haemorrhage. No severe bleeding was reported in the open label caplacizumab group. Overall, bleeding events requiring therapeutic intervention were reported in 14 patients (19.7%) in the caplacizumab group, compared with 2 patients (2.7%) in the placebo group.

6.36 A summary of complications relating to plasma exchange is presented in Table 16.

Table 16: Summary of plasma exchange complications in HERCULES (post-hoc analysis): mITT

	n	Caplacizumab n with events (%)	n	Placebo n with events (%)
Any treatment-emergent adverse event related to plasma exchange				
Initial (DB) treatment period	71	24 (33.8)	73	30 (41.1)
During daily plasma exchange	71	24 (33.8)	73	29 (39.7)
Post-daily plasma exchange	65	0	64	2 93.1)
Open label treatment period	2	1 (50)	26	10 (38.5)
During daily plasma exchange	2	1 (50)	26	8 (30.8)
Post-daily plasma exchange	2	0	23	4 (17.4)
Overall treatment period	71	25 (35.2)	73	34 (46.6)
Follow-up period	68	1 (1.5)	61	0
Overall study period	72	25 (34.7)	73	34 (46.6)

Source: Table 14.2.1.6.5.1, p.1 't14_2_1_6_5_1_TEAE_Rel_PEX_Complications_v0.1, Attachment 7 of the submission

6.37 The analysis shows a trend towards reduced plasma exchange complications associated with treatment with caplacizumab compared to placebo. However, this was performed post-hoc and should be interpreted with caution. Further, due to the crossover to caplacizumab and the potential for a protocol-driven increase in plasma exchange duration in the placebo arm, this difference is difficult to interpret.

Benefits/harms

6.38 Of the 145 patients in the HERCULES trial population, 72 of whom were randomised to caplacizumab and 73 to placebo, over the double blind treatment period (average duration 24 and 37 days in placebo and caplacizumab arms respectively), treatment with caplacizumab was associated with:

- No difference in the number of days to platelet normalisation
- Approximately one less day of plasma exchange; and
- Approximately 1.3 fewer days in hospital.

6.39 On the basis of the direct evidence presented in the submission (HERCULES), every 100 patients with acquired thrombotic thrombocytopenic purpura who are treated with caplacizumab in combination with standard of care, compared with standard of care alone (plasma exchange plus immunosuppression), over an approximately 24-37 day period, would result in:

- Approximately 37 fewer patients with either TTP-related death, recurrence of TTP or major thromboembolic event, primarily due to a difference in recurrence of TTP (approximately 34 fewer patients); and
- No difference in major thromboembolic events such as myocardial infarction and stroke.

6.40 On the basis of the direct evidence presented in the submission (HERCULES), every 100 patients with acquired thrombotic thrombocytopenic purpura who are treated

with caplacizumab in combination with standard of care, compared with standard of care alone (plasma exchange plus immunosuppression, with crossover to caplacizumab after disease recurrence in 36% of patients), over an approximately 29 and 37 days treatment period with study drug in placebo and caplacizumab arms respectively, with 28 days additional follow up, would result in:

- Approximately 23 more patients with any bleeding event related to the study drug;
- Approximately 7 more patients with a serious bleeding event (requiring intervention); and
- Approximately 14 more patients with headache.

Clinical claim

6.41 The submission described caplacizumab 10 mg daily in combination with standard of care as superior in terms of effectiveness, and inferior in terms of safety compared with standard of care alone for the treatment of aTTP. The submission also stated that in the treatment of adult patients with an acute episode of aTTP, caplacizumab results in a decrease in the time to platelet normalisation and a reduction in the risk of the composite endpoint of aTTP-related death, aTTP recurrence or major thromboembolic events.

6.42 The ESC considered the claim of superior efficacy of caplacizumab versus standard of care was primarily supported by a reduction in the risk of recurrence. The ESC noted however, that this outcome could be confounded, and is dependent on the extent of use of rituximab in clinical practice, which as noted above has also shown to reduce the risk of relapse.

6.43 The statistically significant difference in time to platelet normalisation was interpreted by ESC to be clinically meaningful if it resulted in a reduction in the number of days on PEX. The ESC noted that mean days on PEX during the double-blind period was reduced by one, with no difference in the median days; however, there was wide variation in days on PEX (see standard deviations and ranges in Table 13). The median days to platelet moralisation (0.19) and the wide confidence intervals for the hazard ratio (HR of 1.55; 95% CI: 1.095, 2.195) made the clinical importance of these results unclear.

6.44 There is limited information around the treatment effect of caplacizumab on long-term sequelae associated with aTTP. Although resolution of thrombocytopenia is a standard end point for plasma exchange in patients with aTTP, the relationship between faster normalisation of platelet counts and the long-term sequelae of aTTP is unclear. As stated above, the ESC considered it would be reasonable to assume that the better and faster you control microangiopathic events initially, the less long-term sequelae would be experienced; however the ESC noted this is not well documented

and the trials were limited by small patient numbers and lack of long-term follow-up data.

6.45 Uncertainties still remain regarding the benefit-risk in treatment of longer duration than investigated in the studies. Further, no data on re-treatment is currently available.

6.46 The ESC considered the claim of inferior safety was appropriate given the increased risk of bleeds, including severe bleeds, and headache.

6.47 The PBAC considered the claim of superior comparative effectiveness was supported in relation to slightly faster time to platelet normalisation and reduction in haematological aTTP recurrence.

6.48 The PBAC considered the claim of inferior safety was appropriate.

Economic analysis

6.49 The ESC considered a cost-effectiveness/utility analysis was appropriate based on the statistically significant reduction in recurrence of TPP in the caplacizumab arm versus best supportive care. However, the ESC acknowledged the clinical importance of this result was unclear. The ESC further advised that the long-term clinical benefit was unclear and that further clinical input was required to improve the model structure.

6.50 The submission presented a stepped economic evaluation of caplacizumab compared with standard of care for the treatment of acquired thrombotic thrombocytopenic purpura (aTTP). The economic model was based on survival benefit derived from combined HERCULES and TITAN trial data and a retrospective observational study of acute aTTP episodes, extrapolated to 60 years. Other modelled inputs were largely based on HERCULES trial data and assumptions. The economic evaluation was presented as a cost-effectiveness/utility analysis.

Table 17: Summary of model structure, key inputs and rationale

Component	Description
Type of analysis	Cost-effectiveness/cost-utility analyses
Outcomes	LYs, QALYs
Time horizon	60 years in model base case versus median treatment duration of 35 days in the overall treatment period (double-blind and open-label periods) of the HERCULES trial
Methods used to generate results	Markov cohort model
Cycle length	3 months, half-cycle corrections applied to both costs and outcomes

Health states	The Markov model contains 7 health states, distributed over 2 model phases:
	• Acute aTTP episode (1st model cycle)
	  ○ No acute MI/stroke
	  ○ Acute MI
	  ○ Acute stroke
	• Chronic remission (subsequent cycles)
	  ○ No prior MI/stroke
	  ○ Post MI
	  ○ Post stroke
	• Dead (patients can transition from either acute or chronic health states)

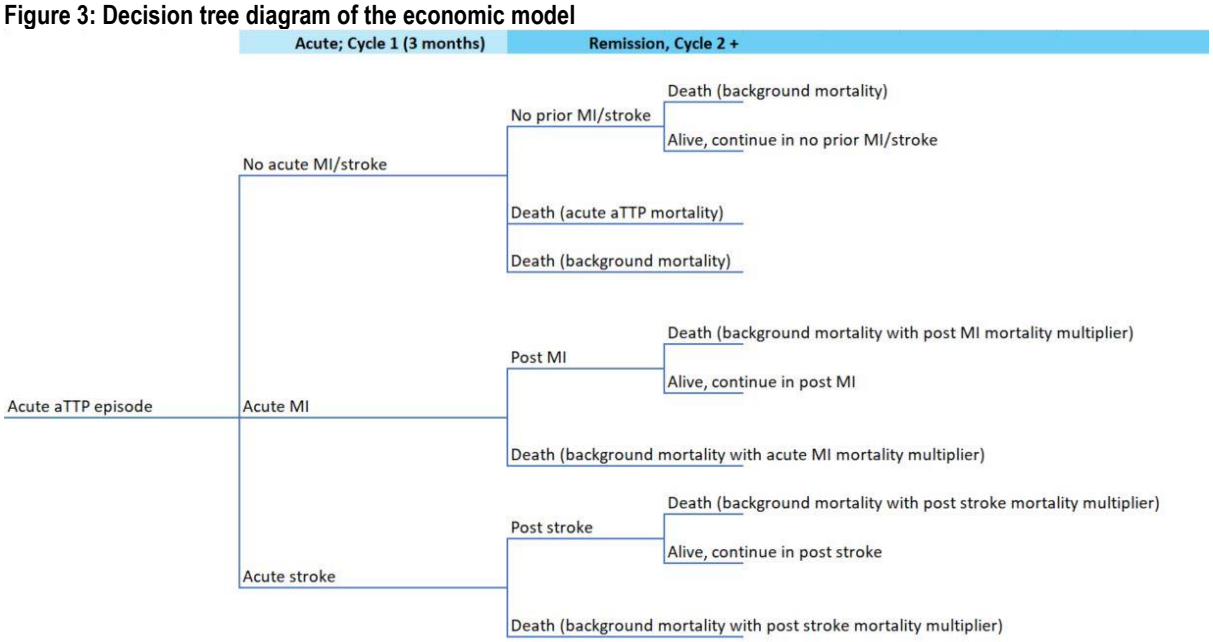
Transition probabilities	Transition probabilities in the first 3-month cycle were derived using the probability of death due to an acute aTTP episode and the incidence of MI and stroke from the HERCULES trial (post-hoc analysis of double-blind period). The probability of aTTP-related death was derived separately for each arm. For caplacizumab, the death rate was derived using combined data from the HERCULES and TITAN trials. For SOC, the death rate was based on a retrospective study of aTTP mortality from the UK TTP registry (Alwan 2017). There were no death transitions in the first cycle. The submission assumed all deaths related to acute events (aTTP-related, MI and stroke) occurred after the first cycle. Deaths due to aTTP were attributed to patients in the no MI/stroke health state. The probabilities of death due to MI or stroke were derived using mortality multipliers for MI (SOLVD 1992 heart failure study), stroke (FUTURE study of TIA and stroke, Rutten-Jacobs 1993) and background mortality (general population mortality estimates from ABS 2016-2018 Life Tables). The distribution of patients across chronic health states in the second cycle was based on patients remaining alive from each acute health state after accounting for aTTP-related death, death due to acute MI or stroke and background mortality. In subsequent cycles, all patients in the no prior MI/stroke health state either remain in their health state or die due to background mortality. All patients in the post MI or post stroke health states either remain in their respective states or die of increased mortality due to MI or stroke.
Health related quality of life	No acute MI/stroke utility: caplacizumab, 0.841; SOC, 0.827 Acute MI utility: caplacizumab, 0.336; SOC, 0.331 Acute stroke utility: caplacizumab, 0.528; SOC, 0.520 The baseline aTTP utility (applied to no acute MI/stroke health state) in each arm was derived using a complex, multi-step approach incorporating general population utility estimates (EQ-5D-5L) and 3-month QALY decrements due to the acute aTTP episode. QALY decrements were derived using published disutilities (EQ-5D-3L) for other disease areas for an assumed set of events, HERCULES trial data and assumptions. The acute MI and stroke utilities were calculated using utility multipliers for MI and stroke published in draft guidance for lipid modification for cardiovascular disease (NICE February 2014). The MI utility multiplier was further adjusted in the submission based on an assumed

Component	Description
	distribution across 3-monthly periods in the first year. The multipliers were applied to the baseline aTTP utility. No prior MI/stroke utility: 0.879 decreasing to 0.829 Post MI utility: 0.774 decreasing to 0.730 Post stroke utility: 0.552 decreasing to 0.521 The no prior MI/stroke utility was assumed based on age- and gender-adjusted general population EQ-5D-5L utility values (McCaffrey 2016). The post MI and stroke utility values were calculated using utility multipliers for MI and stroke published in draft guidance for lipid modification for cardiovascular disease (NICE February 2014) and general population utility estimates.
Health resource use and costs	Caplacizumab drug cost was estimated based on circumstances of use in the HERCULES trial including a proposed 3-vial cost offset (35.6 vials) and the proposed effective AEMP $[redacted] per vial. Treatment and disease management costs for the acute aTTP episode for caplacizumab ($[redacted]) and SOC ($[redacted]) included costs associated with plasma exchange, hospitalisation (acute ward), ICU stay, rituximab drug and administration, ADAMTS13 tests and specialist visits. Costs associated with plasma exchange, hospitalisation and ICU stay were estimated using AR-DRG items and estimated use during the HERCULES trial. Rituximab drug and administration costs (outpatient costs only) were estimated using the DPMA for 800 mg doses, infusion costs based on MBS item for 1 hour or less, and assumed circumstances of use. The ADAMTS13 test cost was based on the sponsor's survey of Australian test centres and assumed frequency. Specialist visit costs (outpatient costs only) were based on the relevant MBS item and assumed frequency. Acute MI health state costs ($1,693) were based on Australian data from the COSMIC study (Ioannides-Demos 2010). Acute stroke health state costs ($7,102) were based on Australian data from the NEMESIS study (Cadilhac 2009). Estimates were inflated to 2020 costs using the ABS Consumer Price Index. There were no costs for patients in the no acute MI/stroke health state. Post MI health state costs ($761) were based on Australian data from the LIPID trial (Glaziou 2002). Post stroke health state costs ($1,451) were based on Australian data from the NEMESIS study (Cadilhac 2009). Estimates were inflated to 2020 costs using the ABS Consumer Price Index. There were no costs for patients in the no prior MI/stroke health state.

Source: Section 3.3, p 123; Section 3.4, p 127; Section 3.5, p 137; Section 3.6, p 142 of the submission
Abbreviations: AR-DRG, Australian Refined – Diagnosis Related Groups, EQ-5D-3L, EuroQol 5-dimension 3-level quality of life questionnaire; EQ-5D-5L, EuroQol 5-dimension 5-level quality of life questionnaire

6.51 The Markov model structure included 7 health states distributed between an acute aTTP episode (initial 3-month cycle) and chronic remission (subsequent 3-month cycles until 60 years). A decision tree of the model is presented in the figure below.

Figure 3: Decision tree diagram of the economic model



Source: constructed during the evaluation using 'Cablivi+PBAC+Section+3+CEA_March+2020' Excel workbook, Attachment 7 of the submission

6.52 It was difficult to interpret the submission's assumption of no deaths in the first cycle and implementation of acute event deaths (aTTP mortality, acute MI mortality, acute stroke mortality) in the second cycle, due to poor documentation. During the evaluation, alternative adjustments to death transitions were tested which appeared to have a limited impact on the results of the economic analysis. The ESC considered the assumption of no deaths in the acute phase (first three month cycle) was inconsistent with the underlying data presented (Alwan 2017), suggesting a median time to death of four days (range: 1-39 days) from initial presentation of symptoms.

6.53 The submission assumed no long-term costs and consequences due to the acute aTTP episode aside from MI or stroke events. The ongoing benefit due to caplacizumab treatment was driven by aTTP-related deaths during the acute episode, with events due to MI and stroke having minimal impact. The ESC considered that although stroke and MI are rare events, they are clinically important in the context of TTP and are associated with high morbidity and mortality. However, the inclusion of MI and stroke and no other events, such as pulmonary embolism and DVT was not justified. Data from the included trials did not support a difference in the occurrence of major thromboembolic events between treatment arms.

6.54 The ESC noted the modelled extrapolation resulted in substantial prolonged benefits in the caplacizumab arm, driven by a greater number of patients remaining in the no prior MI/stroke health state compared to standard of care, with no ongoing costs or consequences. The ESC considered the extrapolation of treatment benefit beyond the

trial duration was inadequately supported by clinical evidence in the submission. A trial-based analysis may have been more appropriate.

6.55 The ESC considered the model structure did not adequately capture the long term consequences of events occurring in the acute phase. The ESC noted the structure did not allow for subsequent events or relapses, which was inconsistent with the evidence presented, which suggested recurrence occurred in close to 40% of patients following their initial presentation of aTTP in the placebo arm. The ESC noted the increased risk of multiple long-term health issues, related to an acute episode of aTTP in patients who had recovered was not captured in the model. The ESC noted the long-term consequences were only present via the acute MI/stroke health states and these had almost no impact on the modelled outcome.

6.56 The baseline aTTP utility estimate was dependent on the assumption that general population utility was representative of the modelled population prior to the acute aTTP episode. This was inconsistent with baseline characteristics from the HERCULES trial with documentation of some patients having significant co-morbidities (e.g. prior history of thromboembolic events, concurrent immune system disorders, prior history of splenectomies). The ESC considered the baseline aTTP utility estimate did not meet face validity.

6.57 There was no justification provided in the submission for the selection of events used to capture consequences of an acute aTTP episode (pulmonary embolism, deep vein thrombosis, plasma exchange complications, aTTP hospitalisation, treatment-related serious bleeding). The selection of outcomes appears to be based on a limited number of events captured in the HERCULES trial that may not be a comprehensive representation of other clinically significant events related to severe thrombocytopenia, tissue ischaemia and organ dysfunction (e.g. renal failure).

6.58 The submission inappropriately applied a 3-month QALY decrement due to other events to the general population utility estimate to derive a baseline aTTP utility. In the model, there was a further adjustment for the model cycle when calculating total QALYs (i.e. divided by 4 again), which resulted in very small QALY decrements due to these events. Overall, the estimated utility did not meet face validity.

6.59 The ESC agreed with the evaluation that the utility value for an acute MI lacks face validity as it appears significantly worse than the utility value for an acute stroke. This was due to the use of an acute MI multiplier that was inappropriately derived in the submission.

6.60 The submission assumed that patients in the no prior MI/stroke health state have the same utility as the general population. There were no data provided in support of this assumption. The submission did not account for increased baseline risk in the modelled population due to co-morbidities and potential long-term consequences in individuals who have recovered from an episode of aTTP. The ESC considered that overall, the approach favoured caplacizumab.

6.61 The estimated utility values for the post MI and post stroke health states were derived using utility multipliers for patients with cardiovascular events (MI or stroke) that may not be similar to the aTTP population in the model. It was not appropriate to assume utility decrements solely due to presence of MI or stroke as there are likely differences in patient characteristics apart from cardiovascular disease.

6.62 The submission assumed the circumstances of use of caplacizumab in the HERCULES trial were generalizable to the requested PBS population. The estimated use of caplacizumab was primarily driven by mean treatment duration during the double-blind treatment period of the trial, which may be affected by lower rates of rituximab use and shorter durations of plasma exchange than expected in clinical practice. Treatment durations were variable between patients, with wide-ranging estimates within the double-blind period (median 35.0 days; range: 1 to 65 days). The ESC considered the extent of the generalisability of the trial population to the requested PBS population remained uncertain, particularly given the varied and unknown extent of use of rituximab in Australian clinical practice.

6.63 In the trial, patients had one session of plasma exchange prior to randomisation. As mean treatment duration reported in the trial was based on on-study treatment, the calculated number of vials in the submission did not account for caplacizumab use (one dose) alongside the first plasma exchange session.

6.64 The submission assumed that the trial-based estimates of use were applicable to the 3-month duration of the initial cycle. The estimated use of caplacizumab was calculated based on variable utilisation during the initial plasma exchange period, potential weekly treatment extensions (up to 30 days) and a relatively small number of patients with exacerbations who re-initiated treatment. The submission did not account for patients who relapsed during the 1-month follow up (6/71 patients, 8.5%). The management of relapses in practice was unclear.

6.65 The drug cost was offset by 3 vials, based on a proposed arrangement that caplacizumab will be provided at no cost prior to confirmation of diagnosis via ADAMTS13 testing. The number of vials was estimated based on an assumed time lag between treatment initiation and test results. A survey of testing centres in Australia suggested turn-around times of between 24 hours and 7 days, depending on the urgency of the request. The model was moderately sensitive to the estimated use of caplacizumab and proposed offset.

6.66 The submission assumed the use of plasma exchange and duration of hospitalisation from the HERCULES trial was applicable to clinical practice. It was difficult to interpret data from the overall treatment duration, which includes additional resource use during the open-label caplacizumab period, analysed by initial randomisation. The results suggested differential use between treatment arms, which was largely driven by increased exacerbations and re-initiation of plasma exchange in the placebo arm (26 placebo patients and 2 caplacizumab patients). The increased exacerbations may

be a consequence of protocol-driven use of plasma exchange, which was shorter than expected in clinical practice. Results based on the double-blind period suggest smaller differences in durations of plasma exchange and hospitalisation between treatment arms.

6.67 Resource use associated with general hospitalisation, ICU stay and plasma exchange were inappropriately applied as mutually exclusive items in the model. In practice, there is likely to be overlap between costs associated with plasma exchange and hospitalisation. It was unclear from the trial report whether ICU stay and general hospitalisation were independent measures.

6.68 Estimated health state costs for MI or stroke in the acute and chronic phases were derived from relatively old data that may not represent current clinical practice and/or health resource costs. Overall, these health state costs had limited impact on the economic analysis due to the relatively small number of cardiovascular events.

6.69 Key drivers of the economic model are summarised in the table below.

Table 18: Key drivers of the model

Description	Method/Value	Impact
Modelled survival benefit	The probability of death from an acute aTTP episode for caplacizumab (0.93%) was based on a crude death rate calculated using combined data from the caplacizumab arms of the HERCULES and TITAN trials. This estimate should not be considered reliable as data from the included trials were insufficient. The numerical difference in deaths between arms in the HERCULES trial was based on a relatively small number of deaths, and there were multiple concerns with the conduct of the TITAN trial that was prematurely terminated due to recruitment challenges. The submission claimed the trial-based mortality data for the placebo arm may not be representative of standard of care due to treatment-switching during the open-label period of HERCULES. The submission claimed that a retrospective study of acute aTTP episodes provided the most reliable estimate of mortality risk for SOC as it was based on a relatively large dataset (N=312 episodes involving 292 patients), had more recent data capture (2009 to 2016) and was conducted in a similar healthcare setting (UK) to the Australian system (Alwan 2017). Results from the Alwan 2017 study suggests an overall mortality rate of 10.26% (n = 32 deaths out of 312 episodes). The assumed timing of aTTP-related deaths in the model (during the second 3-month cycle) was inconsistent with data the Alwan 2017 study suggesting a median time to death of 4 days (range 1-39 days) from initial presentation. There were concerns with the generalisability of the mortality rate to the modelled population due to differences in the distribution of initial versus recurrent patients, and limited reporting of other prognostic factors (e.g. co-morbidities, history of thromboembolic events), disease management and interventions used in the registry dataset. The submission noted the developers of the global economic model conducted a literature review of mortality due to aTTP based on 127 trials (data not provided). The submission stated that mortality rates varied widely across these studies, ranging from 0 to 57%. Results from a meta-analysis of the data suggested an overall mortality rate of 13.2% (95% CI: 11.9%, 14.5%) during the acute phase of the disease. However, the submission claimed the meta-analysed results were limited by	High, favours caplacizumab

Description	Method/Value	Impact
	concerns with heterogeneity of patient populations and small patient numbers informing mortality rates. These results could not be validated as the literature review and meta-analysis were not provided in the submission Based on the mortality rates used in the model, the submission assumed a 91% reduction in mortality due to the addition of caplacizumab to standard of care. The assumed magnitude of survival benefit with caplacizumab treatment was larger than the numerical difference calculated in the submission using exploratory data from the included trials. No data were provided in support of this assumption. The model was sensitive to the magnitude of survival benefit attributed to caplacizumab. The ESC considered the mortality benefit in the model was unreliable.	
Extrapolation	The modelled survival difference between treatment arms due to the acute aTTP episode informed the proportion of patients entering the chronic remission health states in the second 3-month cycle. All patients entering the chronic remission health states (no prior MI/stroke, post MI, post stroke) were assumed to remain in those health states or die of background mortality. Patients in the post MI and stroke states were at increased risk of mortality due to the acute MI or stroke event. There were no data provided in support of the assumed transition probabilities in the chronic remission state. The model structure did not allow for subsequent events or relapses, which is inconsistent with the potential for relapses (30-40%) in the majority of patients who are relatively young at initial presentation. MI and stroke events had a limited impact on the results of the economic analysis due to a relatively small number of events in the model. The submission assumed that patients who did not have an MI or stroke have the same mortality rate as the general population. There were no data provided in support of this assumption. The submission did not account for increased baseline risk in the modelled population based on the HERCULES trial, with documentation of some patients having significant co-morbidities (e.g. prior history of thromboembolic events, concurrent immune system disorders, prior history of splenectomies). Long-term follow-up observations have documented increased risks for multiple health problems in individuals who have recovered from an episode of aTTP. These risks include minor cognitive impairment, major depression, hypertension, abnormal kidney function, and development of systemic lupus erythematosus. Overall, the submission's approach was in favour of caplacizumab as a greater proportion of patients remain in the no prior MI/stroke state compared to SOC, with no ongoing costs or consequences.	High, favours caplacizumab

Source: Constructed during the evaluation

6.70 The results of the modelled economic evaluation are summarised below.

Table 19: Results of the stepped economic evaluation

Step and component	Caplacizumab	SOC	Increment
Step 1a: Mortality data based on the overall study period of the HERCULES trial (caplacizumab 1.41%, SOC 4.10%), caplacizumab drug costs based on the double-blind period of the HERCULES trial			
Costs	$[redacted]	$0	$[redacted]
Deaths	0.0141	0.0410	-0.0269
Incremental cost/death avoided			**$**[redacted]

Step and component	Caplacizumab	SOC	Increment
Step 1b: Mortality data based on combined overall study periods of the HERCULES and TITAN trials (caplacizumab 0.93%, SOC 4.46%), caplacizumab drug costs based on the double-blind period of the HERCULES trial			
Costs	$	$0	$
Deaths	0.0093	0.0446	-0.0353
Incremental cost/death avoided			**$**
Step 1c: Mortality data for caplacizumab based on the combined overall study periods of HERCULES and TITAN trials (0.93%) and for SOC based on Alwan 2017 retrospective study (10.26%), caplacizumab drug costs based on the double-blind period of the HERCULES trial			
Costs	$	$0	$
Deaths	0.0093	0.1026	-0.0933
Incremental cost/death avoided			**$**
Step 2: Assume mortality data and caplacizumab drug costs are applicable to a 3-month time horizon (deaths occur at the start of the cycle, no half-cycle correction)			
Costs	$	$0	$
LYs	0.2477	0.2244	0.0233
Incremental cost/LY gained			**$**
Step 3: Add treatment and disease management costs (hospitalisation, ICU stay, plasma exchange, ADAMTS13 tests, specialist visits, rituximab drug and administration costs) based on HERCULES trial data (double-blind and open-label periods) and assumptions			
Costs	$	$58,540	$
LYs	0.2477	0.2244	0.0233
Incremental cost/LY gained			**$**
Step 4: Include probabilities for acute MI and stroke based on HERCULES trial data (double-blind period) which were adjusted for deaths due to aTTP, add costs due to acute MI and stroke events			
Costs	$	$58,823	$
LYs	0.2477	0.2244	0.0233[a]
Incremental cost/LY gained			**$**
Step 5: Extrapolate to 60 years: Include transition probabilities to no prior MI/stroke health state, post MI and post stroke health states; assume all deaths (due to aTTP, acute stroke and MI) occur during second cycle, include background mortality and increased mortality due to post MI or stroke (from second cycle), add half-cycle correction			
Costs	$	$65,513	$
LYs	38.037	34.311	3.726
Incremental cost/LY gained			**$**
Step 6: Add post MI and post stroke health state costs			
Costs	$	$72,442	$
LYs	38.037	34.311	3.726
Incremental cost/LY gained			**$**
Step 7: Include health state utility values			
Costs	$	$72,442	$
QALYs	32.591	29.272	3.32
Incremental cost/QALY gained			**$**
Step 8: Apply 5% discount rate to costs and consequences			
Costs	$	$67,834	$
QALYs	14.185	12.768	1.416
Incremental cost/QALY gained (base case)			**$**

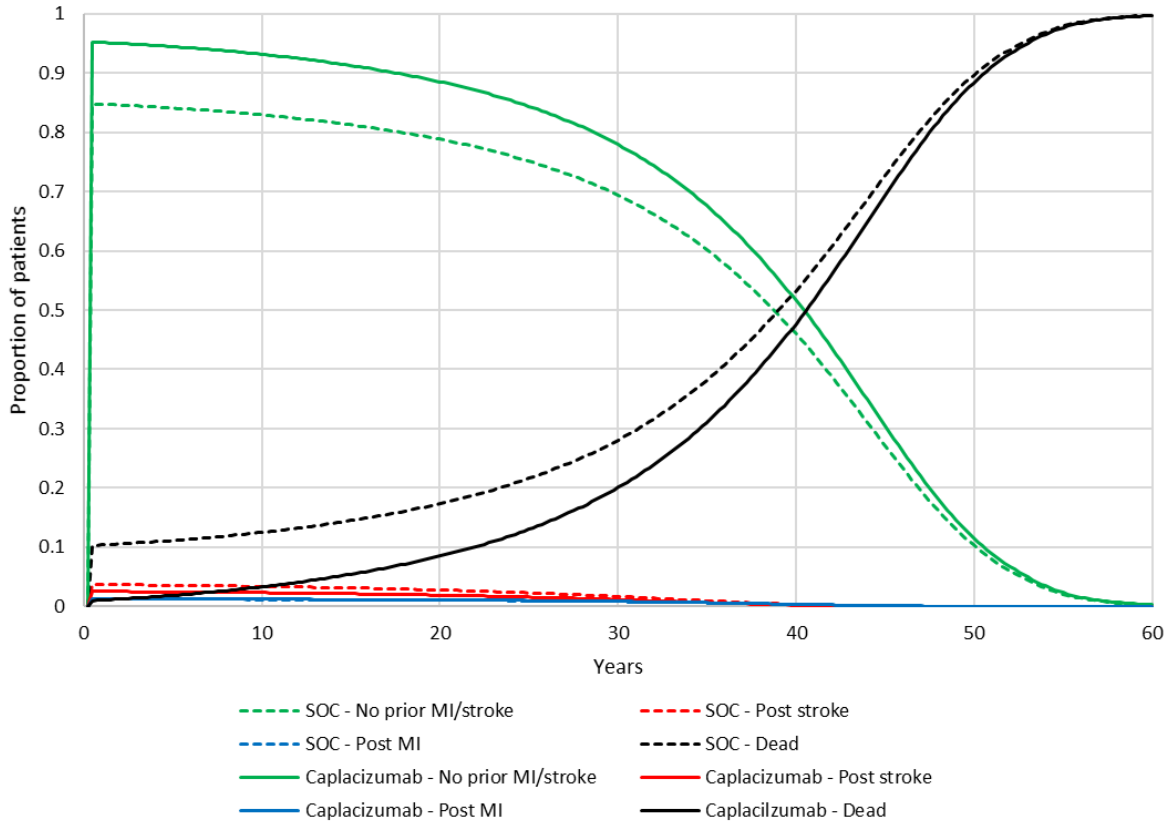
Source: Table 3.8.2, p 154 and 'Cablivi+PBAC+Section+3+CEA_March+2020' Excel workbook, Attachment 7 of the submission
Abbreviations: LY, life years; QALY, quality adjusted life years
[a] There was no change to cumulative life years in both arms as the submission assumed no deaths due to cardiovascular events in the first cycle

6.71 The modelled survival benefit with caplacizumab treatment during the acute aTTP episode and extrapolation to 60 years had the largest impacts on the stepped economic evaluation.

6.72 Based on the economic model, treatment with caplacizumab was associated with a cost per QALY gained of $75,000 to < $95,000 compared with standard of care. The ESC agreed with the evaluation that the cost-effectiveness estimate should not be considered reliable as extrapolated benefits to 60 years were based on limited mortality data from the trials combined with mortality rates from the Alwan 2017 study, an assumed survival benefit with caplacizumab and inadequately supported assumptions regarding long-term consequences.

6.73 The figure below illustrates the distribution of patients in each health state (no acute MI/stroke, acute MI, acute stroke, no chronic MI/stroke, chronic MI, chronic stroke, dead) over the model duration.

Figure 4: Markov trace of no prior MI/stroke, post stroke, post MI and total death



Source: Constructed during the evaluation using 'Cablivi+PBAC+Section+3+CEA_March+2020' Excel workbook, Attachment 7 of the submission
Abbreviation: MI, myocardial infarction

6.74 The Markov trace shows that while the treatment effect of caplacizumab was in the initial cycle, the ongoing consequences of remaining in the no prior MI/stroke health state from Cycle 2 (6 months) resulted in a substantial prolonged benefit. The ongoing

benefit was driven by deaths occurring due to the acute aTTP episode, with events due to MI and stroke having a minimal impact. The ESC considered that the modelled survival benefits due to caplacizumab treatment were inappropriately derived and insufficiently supported by the limited trial data. No data were provided in support of changes to long-term consequences when adding caplacizumab to standard of care during the acute aTTP episode.

6.75 The results of key sensitivity analyses are summarised below.

Table 20: Results of sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER
Base case	**$**	**1.42**	**$**
Time horizon (base case: 60 years)			
1 year	$	0.06	$
2 years	$	0.13	$
5 years	$	0.35	$
10 years	$	0.64	$
20 years	$	1.05	$
50 years	*$*	*1.41*	*$*
Probability of death from the acute aTTP episode (base case caplacizumab: 0.93%, SOC: 10.26%)			
SOC arm based on combined HERCULES and TITAN trial data, caplacizumab assumed (caplacizumab: 0.46%, SOC: 4.5%)	*$*	*0.67*	*$*
SOC arm based on sponsor's meta-analysis (not provided), caplacizumab assumed (caplacizumab: 1.20%, SOC: 13.2%)	*$*	*1.80*	*$*
SOC arm based on Alwan 2017 study, caplacizumab assumed (caplacizumab: 2.05%, SOC: 10.26%)	*$*	*1.26*	*$*
Combined HERCULES and TITAN trial data (caplacizumab: 0.93%, SOC: 4.46%)	*$*	*0.59*	*$*
HERCULES trial (caplacizumab: 1.41%, SOC: 4.10%)	*$*	*0.47*	*$*
TITAN trial (caplacizumab: 0%, SOC: 5.1%)	*$*	*0.82*	*$*
Effective price of caplacizumab (base case: AEMP $ per vial)			
10% price reduction (AEMP $ per vial)	*$*	*1.42*	*$*
10% price increase (AEMP $ per vial)	*$*	*1.42*	*$*
Number of vials used to estimate caplacizumab drug cost (base case: 35.6 vials, including 3 vial cost offset)			
38.6 vials, without cost offset	*$*	*1.42*	*$*
37.6 vials, with 1 vial cost offset	*$*	*1.42*	*$*
31.6 vials, with 7 vial cost offset	*$*	*1.42*	*$*
Health resource utilisation during the acute aTTP episode (base case using data from the double-blind and open-label periods of the HERCULES trial: caplacizumab 5.9 days plasma exchange, 9.9 days hospitalisation, 1.33 days ICU stay; SOC 9.5 days plasma exchange, 14.4 days hospitalisation, 3.59 days ICU stay)			
Based on the double-blind period of the HERCULES trial (caplacizumab 5.5 days plasma exchange, 5.5 days hospitalisation, 1.2 days ICU; SOC 6.5 days plasma exchange, 6.8 days hospitalisation, 2.4 days ICU stay)[a]	*$*	*1.41*	*$*
Based on the double-blind period of the HERCULES trial assuming ICU stay is part of total hospitalisation duration (caplacizumab 5.5 days plasma exchange, 4.3 days hospitalisation, 1.2 days ICU; SOC 6.5 days plasma exchange, 4.4 days hospitalisation, 2.4 days ICU stay)[a]	*$*	*1.41*	*$*
No prior MI/stroke utility values (base case: 0.879 decreasing to 0.829 based on age and gender-adjusted general population utility)			
Decrease by 10% (0.791 decreasing to 0.746)	*$*	*1.27*	*$*
Decrease by 20% (0.703 decreasing to 0.663)	*$*	*1.12*	*$*

Source: Table 3.9.1, p161 and 'Cablivi+PBAC+Section+3+CEA_March+2020' Excel workbook, Attachment 7 of the submission

[a] ICU stay estimates were based on initial plasma exchange period only due to relatively small patient numbers in the post-daily plasma exchange period. The duration was weighted using the proportions with ICU stay in the submission (39% in caplacizumab arm and 37% in placebo arm)

Italicised analyses were conducted during the evaluation

The redacted table shows ICERs in the range of $75,000 to < $95,000 to > $1,055,000.

6.76 The results were most sensitive to time horizon, probability of death due to the acute aTTP episode and discounting. Results were moderately sensitive to the effective price of caplacizumab, estimated caplacizumab vial use, health resource utilisation during the acute aTTP episode and the no prior MI/stroke health state utility value.

6.77 The submission noted that costs and consequences associated with MI and stroke events had a minimal impact on the results. This was expected given the relatively small number of events occurring in the model.

Drug cost/patient

6.78 The estimated drug cost for caplacizumab per patient for an acute aTTP episode was $[redacted] based on 35.6 vials (based on HERCULES trial data including the proposed 3-vial cost offset) using the effective AEMP $[redacted] per vial.

6.79 The drug cost per patient for caplacizumab is summarised in the table below.

Table 21: Drug cost per patient for caplacizumab

	Economic analysis	**Financial estimates**
Circumstances of use	Total vial use estimated based on the overall treatment period of the HERCULES trial. Number of vials estimated using mean treatment duration, additional loading dose on Day 1 and proposed 3-vial cost offset.	Total script use estimated based on mean duration of plasma exchange for initial plasma exchange period, post-daily plasma exchange (30 days) and 7-day extended use estimated from HERCULES trial data.
Estimated number of vials	35.6 vials	40.935 vials
Cost per vial (effective)	AEMP $[redacted]	AEMP $[redacted]
Distribution of use across scripts	-	Initial: 100% of patients, 1 script x 4 vials[a] Extended initial: 20% of patients; 5 scripts x 1 vial Post-plasma exchange continuing: 100% of patients, 1 script x 30 vials Extended continuing: 27.8% of patients, 3.05 scripts x 7 vials
Average number of scripts	-	Initial: 1 Extended initial: 1 Post-plasma exchange continuing: 1 Extended continuing: 0.8479
Cost per script (weighted DPMQ)	-	Initial: $[redacted] Extended initial: $[redacted] Post-plasma exchange continuing: $[redacted] Extended continuing: $[redacted]
Cost/patient/episode	**$**[redacted][b]	**$**[redacted]

[a] The number of vials (4) was calculated assuming 6 days of plasma exchange, of which the first 2 days are covered vials provided by the sponsor (3-vial offset)

[b] Calculated as cost per vial (AEMP $[redacted]) x number of vials (35.6)

[c] Calculated as average number of scripts x weighted cost per script (DPMQ)

Estimated PBS usage & financial implications

6.80 This submission was considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial impact for caplacizumab. Key inputs are summarised in the table below.

Table 22: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Australian population	26,301,274 in Year 1 increasing to 28,372,315 in Year 6. Australian Bureau of Statistics population projections for 2021-2026 (3222.0 Series B).	This was appropriate.
Incidence of aTTP	2.72 incident cases per million per year. Estimated from the number of tests with ADAMTS13 <10% from a sponsor-commissioned survey of three laboratories that perform testing for 75% of the Australian population. The size of the denominator (population size) served by each lab was assumed.	The incidence rates were uncertain and relatively low compared with published estimates. There was large variability in incidence reported by each lab surveyed (ranging from 2.07 to 3.83 per million). The true denominator of the serviced population may be overestimated.
Uptake rates	57% in Year 1 increasing to 75% in Year 6. Based on a sponsor-commissioned survey of 8 specialists (16% response rate) expected to treat aTTP episodes. Seven clinicians who had treated 14 patients with aTTP in the past year were surveyed; responses to the question indicated that had caplacizumab been available, they would have used it in the treatment of 8/14 patients (57%).	The generalisability of the uptake rate was uncertain, primarily because it was based on small numbers of clinician responses and treated episodes. The question did not indicate disease severity. Published guidelines and literature suggest that some clinicians may reserve caplacizumab for refractory patients. The survey indicated that some clinicians wouldn't have used caplacizumab at all, and two suggested that they would be selective with caplacizumab
Initial scripts	<500 in Year 1 increasing to <500 in Year 6. All patients assumed to receive one initial script (covering 4 days) to cover the plasma exchange period, post-diagnosis, based on the mean number of days of initial plasma exchange from the HERCULES trial (5.5). The sponsor indicated that they will provide three vials free of charge per patient prior to confirmation of diagnosis via ADAMTS13 testing, allowing for the loading dose and post-plasma exchange dose on day 1, and a subsequent post-plasma exchange dose on day 2. The number of vials (4) was calculated assuming 6 days of plasma exchange, of which the first 2 days are covered vials provided by the sponsor.	The estimated use were based on mean duration of plasma exchange and 100% compliance. This approach is highly dependent upon the results of the HERCULES trial. The duration of plasma exchange within the trial was highly variable (median 5.0 days, range 1-35 days). There is a risk that use of caplacizumab in the HERCULES trial may not reflect use in practice, particularly if there were protocol-driven impacts on the duration of plasma exchange observed in the trial. Further, patients were recruited to the trial one day after plasma exchange was initiated, which was not taken into account in the calculations of mean durations of plasma exchange. The sponsor proposed to supply caplacizumab at no charge until diagnosis of aTTP is confirmed. No reimbursement mechanisms was proposed for this, and this period of time could also be variable depending upon the availability of testing facilities.
Extended initial scripts	<500 in Year 1 increasing to <500 in Year 6. In HERCULES, patients required up to 35 days of plasma exchange. It was estimated that 20% of patients would require extended initial treatment, receiving 5 one-vial scripts (an average of one per patient), based on the assumption that the duration of plasma exchange should be within the standard deviation of 0.94 days of the mean of 5.5 days for 95% of the population.	
Continuing scripts	<500 in Year 1 increasing to <500 in Year 6. Based on the proposed amount (30 vials) for the requested restriction. The submission assumed	While consistent with both the HERCULES trial protocol and the proposed restriction, the vial quantity per script may not be appropriate given

Parameter	Value applied and source	Comment
	100% of patients receive a script for continuing treatment, covering 30 days of treatment following cessation of plasma exchange.	the high cost of caplacizumab. Persistence rates in [redacted] are unclear.
Extended continuing scripts	<500 in Year 1 increasing to <500 in Year 6. The usage for this script (covering 7 days) was based on the proportions of patients needing 1, 2, 3, or 4 additional weeks of treatment in HERCULES; 27.8% patients required an average of 3.05 weeks of additional treatment.	This approach is heavily reliant on the assumption that use in the HERCULES trial will be replicated in clinical practice, and was informed by relatively small patient numbers. The distribution of patients requiring treatment extensions is highly uncertain.

Source: Cablivi+BIM+PBAC+Section+4_March2020 spreadsheet, Attachment 9 of the submission

6.81 The table below presents the estimated use and financial impact of listing caplacizumab on the PBS prepared by DUSC.

Table 23: Revised financial estimates including relapsing patients

	Year 1 (2021)	Year 2 (2022)	Year 3 (2023)	Year 4 (2024)	Year 5 (2025)	Year 6 (2026)
Patient estimates						
Australian population	26,301,274	26,727,025	27,147,199	27,562,195	27,970,435	28,372,315
Number of incident cases per year (2.72 per million)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of incident cases including 10% potential for relapse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients electing treatment (%; from clinician survey)	57%	62%	66%	70%	73%	75%
Total number of patients *(including relapsed)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Script volumes *(including relapsed)*						
Caplacizumab Initial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caplacizumab Extended initial treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caplacizumab Post-plasma exchange continuing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caplacizumab Extended continuing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to PBS (effective) including relapsed patients	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS (effective) excluding relapsed patients	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Cablivi+BIM+PBAC+Section+4_March2020 spreadsheet

Italicised estimates calculated by DUSC Secretariat with the conservative estimate of 10% of TTP/TMA registry patients relapsing

The sponsor's original estimates included offsets for a proposal to provide three vials free of charge per patient prior to confirmation of diagnosis via ADAMTS13 testing. The offsets are not included in the revised estimates presented here.

The redacted table shows that at Year 6, the estimated number of patients was less than 500 and the net cost to the PBS would be between $10 million to < $20 million including relapsed patients and less than $10 million excluding relapsed patients.

6.82 Based on the proposed effective AEMP of $[redacted] per vial, the net cost of listing caplacizumab on the PBS as proposed in the submission is $0 to < $10 million in Year 1 (including cost offset proposed by sponsor of $0.5 million), increasing to $0 to < $10 million in Year 6 (including offset of $0.7 million). The total cost of listing caplacizumab over 6 years is $40 million to < $50 million (including cost offset of $3.4 million). Estimates using published prices are summarised in Attachment 4 of the commentary. The approach used in the submission assumes PBS reimbursement for all caplacizumab scripts dispensed over the course of treating aTTP. Inpatient treatment is not typically subsidised by the PBS, therefore if approved for listing the cost to the PBS may only apply for caplacizumab dispensed during outpatient treatment.

6.83 The utilisation/financial estimates were highly uncertain due to the following issues:

- The size of the eligible population was based on a calculated incidence using testing data from a small number of Australian laboratories and an assumed denominator (population size) serviced by each laboratory. There was large variability in the calculated incidence between labs (2.07 to 3.83 per million per year) and reported in other jurisdictions (between 2-6 million cases per million per year);
- Uptake rates were based on a sponsor-commissioned survey of a small number of clinicians and treated aTTP episodes. The growth of uptake rates over time was assumed. The place in therapy for caplacizumab was unclear as published guidelines and the survey itself suggest that some clinicians may reserve caplacizumab for higher risk patients, such as those refractory to treatment; and
- Estimates of use (script numbers) based on the HERCULES trial are uncertain. There are potential issues with the representativeness of the trial compared with clinical practice, which are likely to impact on treatment durations (e.g. relatively short duration of plasma exchange compared with published estimates). The duration of treatment with caplacizumab in clinical practice is unclear.

6.84 The DUSC considered the estimates presented in the submission were underestimated, mainly due to:

- Utilisation estimate of n=<500 in the first year is based on incident cases with no account for relapsed patients. The Thrombotic Thrombocytopenia Purpura / Thrombotic Microangiopathies Registry managed by Monash University estimates 312 people in Australia currently living with the disease and there is no mention of the potential for these patients to relapse.
- The potential for long term use may not be factored into the financial implications of the submission and may result in a higher percentage of patients utilising the 'extended continuing' restriction than presented in the estimates of the submission.

Quality Use of Medicines

6.85 DUSC commented that the Sponsor's offer of free vials at the beginning of treatment may create a quality use of medicines issue. DUSC commented that free samples offered or supplied to patients/clinicians at the beginning of treatment may be problematic as it can increase prescribing where it may not be clinically appropriate. DUSC considered that the Sponsor should suggest another method to offset the cost of caplacizumab.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of caplacizumab on the PBS for the treatment of acquired thrombotic thrombocytopenic purpura (aTTP). The PBAC considered the clinical place of therapy was uncertain. The PBAC had low confidence in the trial data given trial design, size, and conduct issues. The clinical benefit in the acute setting was considered modest at best and the long-term clinical benefits of treatment remained unclear, given the clinical trial results did not demonstrate a significant improvement in end organ damage and mortality. The PBAC also considered the cost-effectiveness of caplacizumab to be high and uncertain due to the significant structural issues in the economic model, which favoured caplacizumab.

7.2 The PBAC noted that the inpatient component of funding in public hospitals would require joint funding between the Commonwealth, states and territories under the usual National Health Reform Agreement (NHRA) arrangements, with only outpatient treatment eligible for subsidy under the PBS.

7.3 The PBAC noted the eligibility criteria included in the proposed restriction were based on the assessment of haematological markers (e.g. ADAMTS13 activity <10%). The PBAC noted that unlike eculizumab's listing on the PBS for the treatment of patients with a similar condition to aTTP, atypical haemolytic uraemic syndrome (aHUS), the clinical criteria for treatment with caplacizumab did not require the patient demonstrate clinical features of active organ damage or impairment. The PBAC considered this would introduce inconsistencies amongst the PBS eligibility criteria for treatment of thrombotic microangiopathies.

7.4 The PBAC noted the published final draft ISTH Clinical Guidelines placed caplacizumab treatment in the early phase of an acute event of aTTP. While the PBAC acknowledged the clinical need for more targeted therapies to be made available for the treatment aTTP, it considered caplacizumab's place in therapy for use in the acute setting, preventing haematological relapse, or both, remained uncertain.

7.5 The PBAC noted the submission was based on two head-to-head trials (TITAN and HERCULES), comparing caplacizumab in combination with SoC (PEX + immunosuppression), with SoC alone, in patients with symptoms of aTTP who

required treatment with PEX. The primary outcome measured in the trials was time to confirmed platelet count response.

7.6 The PBAC noted several issues with the TITAN study as discussed by the ESC, including: the study was terminated prematurely; 45% of patients discontinued treatment early; a substantial number of ADAMTS13 data was missing; 39% of patients had received prior treatment with PEX (median 18 days); and a number of important analyses were conducted post-hoc (paragraph 6.6). Therefore, the PBAC considered the TITAN trial results were unreliable and could not be used to establish the clinical effectiveness of caplacizumab in the Australian setting.

7.7 The PBAC considered the HERCULES trial should be the primary study used to inform the clinical effectiveness of caplacizumab. However, given there were a number of differences in disease characteristics at baseline between caplacizumab vs placebo (33% vs 53% for recurrent disease, 82% vs 90% for ADAMTS13 <10%) and differences in immunosuppressive medications taken during study period (40% vs 49% on rituximab, 19% vs 6% other), the PBAC considered the overall risk of bias in the HERCULES trial was uncertain but trended towards favouring caplacizumab.

7.8 The PBAC noted caplacizumab resulted in a statistically significant reduction in the time to confirmed platelet count response compared with placebo in HERCULES (HR of 1.55; 95% CI: 1.095, 2.195). The difference in median time to achieve response between treatment arms was not large, being 0.19 days (2.69 vs 2.88), or 1.55 days in the 75th percentile (2.95 vs 4.50).

7.9 The PBAC further noted that during the double-blinded treatment period, treatment with caplacizumab was associated with a statistically significant improvement in the composite endpoint of TTP-related mortality, recurrence, or major thromboembolic event compared with placebo. However it noted that this difference was primarily driven by disease haematological recurrence. Given the higher proportion of patients in the placebo arm with recurrent disease at baseline, the PBAC considered the significance of this result was unclear.

7.10 The PBAC noted there were no appreciable differences between treatment arms in the overall numbers of events in the HERCULES trial. Although there was a numerical trend towards a reduction in some individual events associated with treatment with caplacizumab in the overall study period (stroke), results were based on very small numbers of events and were considered unlikely to be clinically meaningful. The PBAC further considered that a reduction in end-organ damage and/or mortality was a more clinically relevant outcome than haematologically-assessed recurrence.

7.11 Based on the results of the HERCULES trial, the PBAC considered the submission's claim of superior effectiveness of caplacizumab in combination with SoC compared with SoC alone for the treatment of aTTP was supported in relation to slightly faster time to platelet normalisation and reduction in haematological aTTP recurrence, although the PBAC had low confidence in these trial results given the high risk of bias,

the trial design, small size, and conduct issues. The PBAC considered there was little to no evidence suggesting caplacizumab reduced the risk of the major thromboembolic events (end-organ damage), mortality or duration of PEX treatment.

7.12 The PBAC considered the submission's claim of inferior safety of caplacizumab versus SoC was appropriate. The PBAC noted caplacizumab was associated with a number of adverse events, including bleeding-related adverse events, which were reported for 47 patients (66.2%) in the double blind caplacizumab group compared to 36 patients (49.3%) in the double blind placebo group. The PBAC noted two patients in the HERCULES trial experienced serious bleeding related treatment emergent adverse events which were considered at least potentially related to caplacizumab: one case each of subarachnoid haemorrhage and uterine bleeding.

7.13 The PBAC considered the economic evaluation presented was highly uncertain and favoured caplacizumab. The model structure did not adequately capture the long term consequences of events occurring in the acute phase, with cost-effectiveness, with favourable assumptions built into the model, only approached at approximately 50 years following an acute episode. The PBAC agreed with the ESC and considered the economic model structure and inputs required extensive revision. The PBAC noted this would be difficult with the trial data available given the small patient numbers and lack of long-term follow up data.

7.14 The PBAC noted that treatment with caplacizumab was associated with a high cost per QALY gained of $75,000 to < $85,000 compared with SoC. The PBAC further noted the modelled survival benefit with caplacizumab treatment during the acute episode of aTTP and extrapolation to 60 years (significantly beyond the trial duration) had the largest impacts on the stepped economic evaluation (Table 19). Given the extrapolated benefits to 60 years were based on limited mortality data from the trials combined with mortality rates from the Alwan 2017 study, an assumed survival benefit with caplacizumab and inadequately supported assumptions regarding long-term consequences, the PBAC agreed with the ESC and considered the cost-effectiveness estimate should not be considered reliable.

7.15 The PBAC noted the Markov trace (Figure 4) showed the ongoing benefit of remaining in the no prior MI/stroke health state from Cycle 2 (6 months) was driven by deaths occurring due to the acute aTTP episode, with events due to MI and stroke having a minimal impact. The PBAC noted the mortality rates in the model assumed a 91% reduction in mortality due to the addition of caplacizumab to standard of care, which was not supported by the HERCULES trial data. Further, the model did not allow deaths in the acute phase which was inconsistent with underlying data.

7.16 The PBAC also noted the following additional issues related to the economic model:

- The increase in significant bleeding events in patients treated with caplacizumab was not captured in the model;

- The model structure did not allow for subsequent events or relapses, which was inconsistent with the evidence presented, which suggested recurrence occurred in close to 40% of patients following their initial presentation of aTTP in the placebo arm;
- The utility value for an acute MI lacks face validity as it appears significantly worse than the utility value for an acute stroke; and
- The modelled extrapolation resulted in substantial prolonged benefits in the caplacizumab arm, driven by a greater number of patients remaining in the no prior MI/stroke health state compared to standard of care, with no ongoing costs or consequences.

7.17 The PBAC noted the utilisation estimates only accounted for incident patients, while also noting that the Thrombotic Thrombocytopenia Purpura / Thrombotic Microangiopathies Registry managed by Monash University, estimated 312 people in Australia are currently living with the disease and were not accounted for in the utilisation estimates. The PBAC considered the utilisation estimates presented in the submission were very uncertain and most likely underestimated.

7.18 The PBAC agreed with the DUSC that free samples offered or supplied to patients/clinicians at the beginning of treatment may be problematic from a QUM perspective as it may increase prescribing where it may not be clinically appropriate and that the Sponsor should suggest another method to offset the cost.

7.19 The PBAC considered any resubmission should be a major submission and requires:

- New clinical trial data, demonstrating that over time, caplacizumab resulted in an improvement in end organ damage and reduction in mortality;
- More clarity around the appropriate clinical place in therapy for use in the acute setting, preventing haematological relapse, or both;
- A revised economic model, addressing the significant structural issues present in the current model;
- A price reduction to be factored into any revised model; and
- The submission to focus on the PBS-eligible component of treatment, delivered in the outpatient setting

7.20 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

While Sanofi is disappointed at the outcome of the PBAC's consideration of caplacizumab for the treatment of aTTP, we will continue to work with the Committee and the Department to address the areas of uncertainty raised in relation to requested listing in the hope of making this treatment available to Australian patients.