CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0736
Brand name (generic)	CABLIVI (CAPLACIZUMAB)
Indication(s)	Acquired Thrombotic Thrombocytopenic Purpura (aTTP)
Organization	Answering T.T.P. (Thrombotic Thrombocytopenic Purpura) Foundation
Contact information[a]	Name: Sydney Kodatsky

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Answering TTP, in consultation with its members, disagrees with the CADTH recommendation "not to fund" caplacizumab and with their rationale for the following reasons.

1. Caplacizumab works and has saved the lives of Canadians with aTTP when nothing else would work.
2. While CADTH recognizes that TTP is an (ultra-)rare disorder (p.5) affecting 1.7 – 2.2 persons per million, and serious (indeed life-threatening), they nevertheless contend it is possible to conduct "well-designed randomized trial (p. 4), ostensibly even to demonstrate impact on long-term outcomes, namely, relapse rates, organ dysfunction and other disabilities, and mortality/survival (p. 4). Such a trial would require international collaboration, coordination and recruitment across multiple centers to enroll sufficient numbers and, according to the CADTH recommendation, some patients retained in a blinded "no treatment/placebo control" over many years. This scenario is neither feasible nor ethical for many reasons, the most important of which is that other countries who already fund caplacizumab and have established it as standard of care could and would not support a trial with "placebo" group.
3. This reinforces a third point of disagreement with the CADTH recommendation, namely the rejection of Real-World Evidence (RWE) studies. CADTH opined that the "potential for biased patient selection and intergroup differences in measured and/or unmeasured confounding variables [meant that] no firm conclusions could be drawn on the results of these studies." In contrast, at this time, 22 other countries have agreed to fund caplacizumab for treatment of aTTP, drawing partially or wholly on the strength of submitted RWE.

In fact, CADTH collaborator NICE reviewed even less data for caplacizumab (back in 2020) and recommended caplacizumab for reimbursement (https://www.nice.org.uk/guidance/ta667/chapter/1-Recommendations). NICE was able to effectively integrate RWE to supplement shortfalls in RCT in order to put patients' lives first. NICE engaged in a round-table discussion with the leading physicians and the patient group, before finalizing their decision. They noted within their recommendation there was some uncertainty, but the benefit to patients outweighed that. The NICE process was thoughtful and transparent, and should be the same in Canada, if we are truly willing to thoughtfully evaluate rare disease treatments.

TTP is a true outlying rare disease characterized by unpredictable acute episodes that are each considered a medical emergency. This uniqueness makes the evaluation by CADTH of caplacizumab even tougher. Caplacizumab does not target the underlying disease, rather it acts to eliminate the cause of life-altering/ending harm (small blood clots) during crisis (short-term use). Each TTP crisis carries a 30% risk of life-altering complications and/or death from these unpredictable small blood clots, but with access to caplacizumab (designed to stop the dangerous clots until existing treatments can take effect) these risks are much reduced which aligns with our community's desire to survive and resume our lives.

The reality is, we the TTP patients know this drug works. Canadian patients are alive today because of compassionate access to caplacizumab. It has worked in Canada, and it has worked around the world. Since the first review of caplacizumab in 2019, a number of Canadian TTP patients have had access to the drug, and it has minimized devastating long-term and life-altering complications from the small blood clots that characterize a TTP crisis. It protects us, giving standard treatments the opportunity to "kick-in".

*19-year-old **Selena** was suddenly in the ICU stroking without an end in sight. Caplacizumab was added to her treatment and the strokes stopped. She was safe from the blood clots which gave standard therapies the time they needed to kick-in.*
*In January 2021, **Lorraine** suffered a second relapse of TTP after contracting COVID-19 from her dying father who had tested negative days before. Despite receiving standard TTP treatment, Lorraine's case seriously worsened and she became very scared that maybe she would not dodge the bullet this time. Caplacizumab was added to her treatment regime and she was released from the hospital two weeks later, requiring half the time in hospital as her first two TTP episodes.*
***Yhulan**, a child and youth worker in Toronto, was rushed by ambulance to hospital with her 3rd TTP relapse in critical condition. She was intubated for a week in the ICU. Only after caplacizumab was added to her treatment regiment did her case turn around.*

On Real-World Evidence (RWE):
• This submission included RWE in addition to the manufacturer's traditional data. While it isn't perfect (RWE never is – it's meant to capture real-world use, not structured trials), it is valuable additional information that proves that caplacizumab works in the real world. Patients like Selena, Lorraine and Yhulan are living proof of its efficacy.
• CADTH notes that RWE has a place in this process, and has communicated the need to include more RWE. We're fully on board with the need to do that. We even understand that CADTH undertook a study and has a current discussion paper out on RWE, and we're pleased to see the system finally moving in this direction. However, TTP patients cannot afford to wait. This time will cost TTP patients lives in Canada.
• Despite the ongoing discussion, this recommendation has shown us truly that RWE isn't being integrated into the evaluation process in a meaningful way.
CADTH notes repeatedly throughout the recommendation that "no firm conclusions" can be made. Indeed, this point is made over and over and feels like a dead end with no recommendation as to how to deal with the lack of conclusive evidence. There is the opportunity to provide "coverage with evidence developing", namely identifying the outcome measures to be collected as "real-world" evidence.
In summary, this recommendation is devastating for our community, and it is well known that a CADTH "no" is the end of the road for TTP patients. Patients like Selena, Lorraine and Yhulan will die waiting for standard treatments to "kick-in". We know from the negative recommendation of caplacizumab in 2019 that the rest of the system (pan-Canadian followed by provinces) won't even acknowledge the file without some sense of a path forward from a CADTH perspective. We urge CDEC to reconsider their stance.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

In our opinion, CADTH was able to generally summarize our patient input, especially around the quality of life issues faced by TTP patients and caregivers, but they failed to understand that we don't expect caplacizumab to reduce relapse rate, and we understand that this is not the purpose of caplacizumab. We believe that CADTH failed to recognize and consider the life-or-death nature of TTP, and the significant risks patients face during a TTP episode, especially during plasma exchange and while waiting for medications to take effect. It must be strongly noted that our desire to survive a TTP crisis is paramount to a treatment that reduces

relapses. We understand that the function of caplacizumab is to keep us safe while standard treatments have time to "kick-in". This caplacizumab "armour" makes every crisis safer. In addition to obvious damage from the small blood clots (stroke, heart attack etc.), research our Foundation supports out of London, ON is investigating the long term effects on the brain that may help understand why so many patients report long term memory and depressive symptoms.
We also believe that CADTH failed to recognize and consider detailed patient perspectives, notably from those who have received caplacizumab. These accounts were included in both the survey (via patient quotes) and via the patient account videos we submitted as part of the input process.
Some of the patients we featured are living proof that caplacizumab has worked within the Canadian medical system in a real-world setting, and yet the recommendation fails to reflect the importance of that.

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒

Simply put, CADTH doesn't see the added value in the real-world evidence presented as part of the submission. We do appreciate the "Discussion Points" (Page 4) element of the recommendation and the associated commentary, despite disagreeing with the contents.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒

The recommendation notes that they have considered implementation issues, but these have not been clearly articulated, nor adequately addressed. Specifically, we note the following:

- The recommendation simply states that CADTH received feedback from drug programs on implementation (p.7), with several different areas – but no details. What was the feedback? Was there discussion on how this therapy could be looked at from a criteria perspective? What was the discussion? As patients, we deserve to know, and be a part of, that discussion.
- CADTH questions the context of the evidence given the Canadian usage of rituximab in clinical practice for TTP patients. Our understanding is that rituximab is routinely provided to TTP patients receiving care in Canada; we would expect that this would continue during caplacizumab treatment as these treatments have different functions. A TTP crisis is a medical emergency. Caplacizumab buys patients time to survive until standard treatments (like rituximab) can "kick-in". Commentary about Canadian use of rituximab and potential benefits is unnecessary.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒

Input was obtained from the drug programs that participate in the CADTH reimbursement review process (p.7). The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for caplacizumab: *Considerations for initiation of therapy ,Considerations for continuation or renewal of therapy, Considerations for discontinuation of therapy, Considerations for prescribing of therapy, Generalizability of trial populations to the broader populations in the jurisdictions, Care provision issues, System and economic issues.* We request CADTH to address each of these issues, namely to propose a process by which patients could be identified as "in need" or "most appropriate" for treatment with capalacizumab, those indicator or outcomes to justify continuing or discontinuing the therapy, how the initial findings could lead to generalize use to the broader population, the necessary management and support, including data collection, from the health providers, and the societal and economic impact of reducing harm and mortality among this population.

The patient community firmly believes that caplacizumab would be effective and cost-effective if available to all aTTP patients that could benefit from it; however, failing this approval at least the subset of patients that can be identified as highest risk and likely to benefit must be provided access. As expressed in the opinion of

the clinical experts consulted by CADTH (p.6), who noted that "caplacizumab may be a reasonable option to be reserved for patients with aTTP recurrence or refractory aTTP as these patients currently have limited treatment options." Not only will caplacizumab have the opportunity to save the lives of these patients (we estimate less than 40 per year across Canada), but treating these patients with caplacizumab is an opportunity to generate more RWE. It must be noted that reserving caplacizumab for the "sickest" patients is not the choice made by peer countries since identifying **each** patient that will suffer irreversible damage or death from unpredictable blood clots is impossible. Unselected patients will inevitably suffer life-altering complications, and some will die despite the existence of preventative treatment.

[a] CADTH may contact this person if comments require clarification.