Answering T.T.P.
Thrombotic Thrombocytopenic Purpura Foundation

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**Trevor Richter**, *Director, CDR and Optimal Use of Drugs*
**Brent Fraser**, *Vice-President, Pharmaceutical Reviews*
**The Canadian Agency for Drugs and Technologies in Health**
*865 Carling Ave., Suite 600,*
*Ottawa, ON Canada K1S 5S8*

Dear Mr. Richter and Mr. Fraser,

On behalf of Canadians who have survived an episode of acquired thrombotic thrombocytopenic purpura (aTTP), Answering TTP Foundation is writing to express our shock and disappointment at the CADTH Canadian Drug Expert Committee (CDEC) recommendation that caplacizumab not be reimbursed for the treatment of adults with aTTP. We wish to emphasize the enormous challenge of rescuing a patient in an aTTP crisis without it.

We request that the decision to not reimburse caplacizumab be reversed. Caplacizumab saves lives and prevents disability. Caplacizumab is the first new treatment developed for aTTP in the last 25 years. Peer nations have recognized its evidence-based utility by updating their international treatment guidelines to include the use of caplacizumab. For a country that pioneered TTP treatment by establishing the effectiveness of plasmapheresis,[1] Canada's unwillingness to adopt caplacizumab is causing undue suffering and death.

ATTP is an ultra-rare, life-threatening emergency that is rapidly fatal without immediate treatment. Even with prompt intervention, many patients face severe long-term consequences due to organ and brain damage from ongoing clotting because it takes time for standard treatments to take effect. Caplacizumab is our only immediate defence, and it works. Once administered, caplacizumab is proven to buy patients time by acting against these potentially life altering clots before they cause further damage.

Plasma exchange and immunosuppression therapy are the current standard treatment for aTTP, but this is not a targeted therapy, and is not without serious side-effects. Plasma exchange is an arduous and time-consuming exchange of a patient's entire volume (or more) of blood plasma through an invasive central line that remains fixed for the duration of treatment. Most patients with aTTP require ICU admission, and nearly half of all Canadian respondents to our patient survey said that they spent more than three weeks, and up to 12+ weeks in hospital. Those are the patients who were lucky enough to survive. **For up to 20% of aTTP patients, the current therapy is insufficient and they die.[2]**

[1] Rock GA et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. N Engl J Med. 1991 Aug 8;325(6):393-7.
[2] Pavenski K et al. Efficacy of Caplacizumab in patients with aTTP in the HERCULES study according to initial immunosuppression regimen. Blood. 2019;134 (Supplement 1): 2365.

Existing treatments are designed to control the underlying mechanism of disease, but require time to take effect, time that aTTP patients do not have. In aTTP, blood clots rapidly form in small blood vessels throughout the body and block the flow of oxygen-rich blood to the body's organs, including the brain, kidneys and heart. Caplacizumab prevents the formation of clots that cause organ damage, allowing patients to survive long enough for existing treatments to take effect.

## Response to CDEC's Published Reasons for the Recommendation

In the CDEC's recommendation report, it states, "*An important outcome identified by patients is a reduction in the risk and rate of experiencing relapses of aTTP. Unfortunately, the design and duration of HERCULES were insufficient to assess the effects of caplacizumab on the rate of relapse beyond the trial's duration.*" While CADTH is correct in its assertion that aTTP patients don't want to suffer a relapse, it is more accurate to focus on the word "risk". **We don't want a relapse to disable or kill us.** Patients need access to caplacizumab because it is the first targeted treatment that addresses the formation of blood clots that are the cause of organ damage, and thus prevents many of the long-term disabilities and death associated with aTTP.

The CDEC report also states that it is not possible to determine the benefit of caplacizumab beyond the duration of the trials. Respectfully, this should not be a barrier to approval because caplacizumab is the only immediate defence available to prevent serious thromboembolic events. Caplacizumab protects patients while standard therapies are given the time required to take effect.

Moreover, organ damage from clots – especially brain damage – is cumulative. If for each relapse caplacizumab reduces the immediate damage, the cumulative beneficial effect of the drug compounds with each cycle of relapse. Caplacizumab is able to reduce the severe impacts of a relapse on organ damage, and we ask that CADTH consider the significant long-term benefit of reducing organ damage at each recurrence.

## Additional Evidence

Two large real-world studies published since the original submission to CADTH confirm the utility of caplacizumab in improving response rate, time to platelet recovery, and reducing organ damage.[3,4] Caplacizumab has also shown to be efficacious in patients with aTTP who had a disease recurrence during double-blind treatment in the HERCULES trial and were switched to open label caplacizumab.[5] A

[3] Coppo P et al. A regimen with caplacizumab, immunosuppression and plasma exchange prevents unfavorable outcomes in immune-mediated TTP. Blood. 2020 Nov 4.
[4] Dutt T et al. Real-world evidence of caplacizumab use in the management of acute TTP. Blood. 2020 Nov 4.
[5] Knoebl P et al. Efficacy and safety of open-label caplacizumab in patients with exacerbations of acquired thrombotic thrombocytopenic purpura in the HERCULES study. Thromb Haemost. 2020;18:2,479-484.

retrospective study in 29 medical centres in Germany further confirmed the effectiveness of caplacizumab during acute disease management.[6]

CADTH's Drug Expert Committee report states that it is unclear if the effects of caplacizumab would be observed in Canadian practice due to the high percentage of patients who received rituximab in the HERCULES study. Further analysis of the HERCULES study data has been published that shows that treatment with caplacizumab improved outcomes in patients with aTTP, irrespective of the type of initial immunosuppressive therapy (i.e. with or without rituximab).[7]

These studies all support the use of caplacizumab in practice across a variety of real-world clinical settings and patient scenarios.

### Alignment with International Recommendations and Standards of Care

It is important to highlight that CADTH's recommendation differs from that of many of our peer nations. To date, caplacizumab has been approved for reimbursement for patients with aTTP in the United States, Austria, Belgium, Denmark, Netherlands, Finland, Italy, and the UK.

In their Technology Appraisal Guidance recommending caplacizumab with plasma exchange and immunosuppression, the National Institute for Health and Care Excellence (NICE) concluded that:

> "Standard care for an acute episode of acquired TTP includes plasma exchange and immunosuppressant medicines. Trial results show that, compared with standard care alone, caplacizumab plus standard care reduces:
>
> - the time it takes to bring platelet levels back to normal
> - the number of plasma exchange treatments needed
> - time in hospital and intensive care" [8]

Recent treatment guidelines published by the International Society on Thrombosis and Haemostasis, and by the multinational Nine-I Network recommend the use of caplacizumab in patients with aTTP.[9,10] Both multidisciplinary guideline panels based their recommendations on systematic reviews of the

[6] Völker LA et al. Real-world data confirm the effectiveness of caplacizumab in acquired thrombotic thrombocytopenic purpura. Blood Adv. 2020;4(13):3085-3092.

[7] Pavenski K et al. Efficacy of Caplacizumab in patients with aTTP in the HERCULES study according to initial immunosuppression regimen. Blood. 2019;134 (Supplement 1):2365.

[8] National Institute for Health and Care Excellence (NICE). Caplacizumab with plasma exchange and immunosuppression for treating acute acquired thrombotic thrombocytopenic purpura. Technology appraisal guidance [TA667] 2020 Dec 16. Available from: www.nice.org.uk/guidance/ta667

[9] Azoulay E et al. Expert statement on the ICU management of patients with thrombotic thrombocytopenic purpura. Intensive Care Med 45. 2019, 1518–1539.

[10] Zheng XL et al. International Society on Thrombosis and Haemostasis (ISTH) guidelines for treatment of thrombotic thrombocytopenic purpura. J Thromb Haemost. 2020 Oct;18(10):2496-2502.

literature, and considered the quality of the studies, the consistency of the results, and directness of the evidence when making their recommendations.

Specifically, current clinical practice guidelines state:

> **"Caplacizumab must be used as a first-line therapy in severe TTP"** (Strength of recommendation: Strong) -*Expert Statement on the ICU Management of Patients with Thrombotic Thrombocytopenic Purpura.* [9]
>
> **"For patients with iTTP experiencing an acute event (first event or relapse), the panel suggests using caplacizumab over not using caplacizumab"** -*International Society on Thrombosis and Haemostasis Guidelines for Treatment of Thrombotic Thrombocytopenic Purpura.* [10]

CADTH's recommendation against the reimbursement of caplacizumab means that Canadian physicians are not able to provide the recommended evidence-based care for their patients consistent with international treatment guidelines.

## Special Considerations: COVID-19

We strongly encourage CADTH to immediately grant an emergency recommendation for the reimbursement of caplacizumab. From a larger health-system perspective, it is important to highlight caplacizumab's ability to reduce the time spent in ICUs, and lessen the overall length of hospital stay. With the COVID-19 pandemic, ICU beds are a critically stressed resource and caplacizumab can help reduce aTTP patients' use of limited resources.

Like COVID-19, aTTP patients cannot be re-scheduled, and they require immediate intensive use of hospital resources. In addition, the immune suppression of standard-of-care therapies puts aTTP patients at extremely high risk for catching COVID-19, further underscoring the need to discharge them from the ICU and the hospital as quickly as possible.

## Conclusion

We recognize that decisions with imperfect data are challenging, and sympathize with the difficulty of the task that CADTH had before it. However, we believe that the Canadian Drug Expert Committee has made a rare error in judgement, and encourage a revisiting and reversal of the reimbursement decision for caplacizumab.

Given the body of clinical evidence showing that caplacizumab successfully addresses an important gap in care until existing therapeutics can take effect, we at Answering TTP respectfully request that CADTH reconsider their decision and recommend the reimbursement of caplacizumab for the treatment of aTTP.

Answering T.T.P.
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Sincerely;

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