# Thrombotic Thrombocytopenic Purpura

CHI Formulary Indication Review

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## Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

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# Abbreviations

| | |
|---|---|
| ADAMTS13 | A Disintegrin-like And Metalloprotease with ThromboSpondin Type 1 Motif No. 13 |
| AICU | Adult Intensive Care Unit |
| aTTP | Acquired Thrombotic Thrombocytopenic Purpura |
| CADTH | Canadian Agency for Drugs and Technologies in Health |
| CHI | Council of Health Insurance |
| cTTP | Congenital Thrombotic Thrombocytopenic Purpura |
| FFP | Fresh Frozen Plasma |
| HAART | Highly Active Antiretroviral Therapy |
| HAS | Haute Autorité de Santé |
| Hb | Hemoglobin |
| HBV | Hepatitis B Virus |
| Hct | Hematocrit |
| HCV | Hepatitis C Virus |
| HIV | Human Immunodeficiency Virus |
| ICU | Intensive Care Unit |
| IQWIG | Institute for Quality and Efficiency in Health Care (Germany) |
| ISTH | International Society on Thrombosis and Haemostasis |
| iTTP | Immune-Mediated Thrombotic Thrombocytopenic Purpura |
| IV | Intravenous |
| KSA | Kingdom of Saudi Arabia |
| LWMH | Low Molecular Weight Heparin |
| NICE | National Institute for Health and Care Excellence (UK) |
| PBAC | Pharmaceutical Benefits Advisory Committee |
| PEX | Plasma Exchange |
| QD | Once Daily |

| | |
|---|---|
| RCT | Randomized Controlled Trial |
| RR | Relative Risk |
| SC | Subcutaneous |
| SD-FFP | Regular Solvent/Detergent Fresh Frozen Plasma |
| SOC | Standard of Care |
| SrCr | Serum Creatinine |
| TMA | Thrombotic Microangiopathy |
| TPE | Therapeutic Plasma Exchange |
| TTP | Thrombotic Thrombocytopenic Purpura |
| UAE | United Arab Emirates |
| UHL | University Hospital Leicester |
| UK | United Kingdom |
| VWF | von Willebrand Factor |

# Executive Summary

Thrombotic thrombocytopenic purpura (TTP) is a rare blood disorder characterized by the formation of blood clots (thrombi) in the small blood vessels throughout the body. These clots can obstruct blood flow to critical organs such as the heart, kidneys, and brain, leading to severe medical complications[1].

TTP, due to the excessive clotting, results in the depletion of blood platelets, which can lead to internal bleeding, bleeding underneath the skin, and other bleeding issues. One manifestation of this bleeding is the development of small red or purple dots known as petechiae, which appear on the skin and resemble a rash. The term "thrombotic" pertains to the formation of blood clots, "thrombocytopenic" indicates a reduced number of platelets in the blood, and "purpura" describes the purplish dots and bruises that manifest on the skin. Other common symptoms include anemia, fever, stroke, jaundice, seizures, headaches, shortness of breath, and tachycardia[1].

TTP is a microangiopathic hemolytic anemia classically characterized by the **pentad** of fever, hemolytic anemia, thrombocytopenia, and renal and neurologic dysfunction[2].

This disease can be categorized into two types: inherited (also called congenital, or cTTP) and acquired or aTTP (also called immune-mediated or iTTP). Inherited TTP is genetically transmitted from parents to their offspring, due to variations in the A Disintegrin-like And Metalloprotease with ThromboSpondin Type 1 Motif No. 13 (ADAMTS13) gene. In contrast, the majority of TTP cases are acquired, meaning that it develops later in life. Acquired TTP (aTTP) occurs when the body mistakenly produces antibodies that inhibit the activity of the ADAMTS13 enzyme, which normally supports blood clotting functions. TTP is sometimes associated with pregnancy and collagen-vascular disease (a group of disorders that affect connective tissue). It also occurs more frequently in people who have HIV[1].

TTP, being a rare disease, occurs in approximately 4 out of 100,000 people each year[1]. Epidemiological research on this matter in the Kingdom of Saudi Arabia (KSA) is limited. Iqbal et al. have reported findings from a single tertiary care center, involving 24 patients, which constitutes the entirety of treated cases in their hospital over an approximately 10-year span from October 2006 to April 2015. This implies that aTTP is also considered rare in the KSA. Experts concur that the estimated incidence of aTTP in Saudi Arabia is approximately 1–2 cases per million[3].

A conservative estimate of the cost of managing a first aTTP event without complications in KSA came to approximately SAR 139,480 (assuming rituximab was not used). When rituximab was used, the cost increased to SAR 183,480. In both cases, the cost of treatments was the main cost driver[4].

Mainstay treatment of TTP is **plasma therapy** (therapeutic plasma exchange (TPE) and fresh frozen plasma infusion), **medications** that can halt or slow anti-ADAMTS13 antibodies formation (rituximab and glucocorticoids), and **surgery** (splenectomy) in severe cases[1]. TTP is considered as an emergency and without treatment, TTP has a 90% mortality rate. However, with proper care, that rate is reduced to 10% to 20%[5].

This report compiles all clinical and economic evidence related to TTP according to the relevant sources. The ultimate objective of issuing TTP guidelines by the Council of Health Insurance is to update the IDF (CHI Drug Formulary) with **the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to patients with TTP in Saudi Arabia**. The main focus of the review was on Saudi, North American, European, and other international guidelines issued within the last five years. In addition, recent systematic reviews and meta-analyses were tackled; thereby providing an in-depth understanding of the different TTP drug therapies and their placement in pharmacological management.

Section 2.0 provides a full description of each pharmacological agent with final statements on the placement of therapy. All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) reflecting specific drug class role in the management of TTP.

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medications in TTP were reviewed and summarized under each drug therapy table in Section 2.0. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC).

Below is a table summarizing the major changes based on the different TTP guidelines used to issue this report:

**Table 1.** General Recommendations for the Management of Thrombotic Thrombocytopenic Purpura (TTP)

| Management of Thrombotic Thrombocytopenic Purpura | | |
|---|---|---|
| **General Recommendations** | **Level of Evidence/Grade of Recommendation** | **Reference** |
| Fresh frozen plasma or cryodepleted plasma are used for plasma exchange. Until plasma exchange can be initiated, plasma infusion (15–30 ml/kg of body weight, daily) | Not graded | KSA and UAE Guidelines 2022[4] |

| | | |
|---|---|---|
| is used. In parallel, corticosteroids (e.g., prednisone) should be used for all patients, bortezomib in refractory patients, and vincristine in relapsed/ refractory patients | | |
| PEX should be started within 4 hours of admission and within of 8 hours of initial diagnosis. | Not graded | NHS Guidelines 2022[6] |
| In parallel, clinicians recommend the use of corticosteroids (e.g., methylprednisolone and prednisolone) and mycophenolate mofetil in all patients, although ciclosporin may be used as an alternative to mycophenolate mofetil.<br>Relapsed/refractory patients are treated with bortezomib. | Not graded | KSA and UAE Guidelines 2022[4] |
| Corticosteroids are administered either as pulse or high-dose therapy (no consensus regarding the superiority of either modality). Both modalities are used as off-label in Japan. | 1B | JAPAN Guidelines 2023[7] |
| The use of caplacizumab in addition to TPE and immunosuppression in confirmed aTTP episodes is recommended. | Not graded | Saudi Arabia Guidelines 2022[8] |
| Caplacizumab is approved by NICE for use in patients with:<br>- Acute acquired, immune TTP (with confirmed ADAMTS13 deficiency)<br>- Age more than 12 years<br>- Weight more than 40kg | Not graded | NHS Guidelines 2022[6] |
| Frontline addition of caplacizumab does not significantly reduce all-cause mortality compared with SOC alone, although it reduces refractory disease risk, shortens time to response, and improves exacerbation rates at the expense of increased relapse and bleeding risk. | Not graded | Caplacizumab systematic review and meta-analysis 2022[9] |
| In Japan, rituximab is indicated for refractory or recurrent TTP only, and its use in the acute phase of TTP is not subject to | 2B | JAPAN Guidelines 2023[7] |

| | | |
|---|---|---|
| national health insurance coverage. However, physicians may consider rituximab for the treatment of patients in the acute phase of iTTP. | | |
| Monoclonal anti-CD20 therapy should be initiated within 3 days of acute iTTP admission | 1B | British Guidelines 2023[10] |
| In patients who have refractory iTTP or have severe ADAMTS13 deficiency despite anti-CD20 therapy, alternative immunosuppressive therapy should be considered | 2B | British Guidelines 2023[10] |
| Splenectomy surgery (grade of recommendation: 2C) and high-dose immunoglobulin (grade of recommendation: 2C) were frequently administered to treat patients with refractory or recurrent TTP. These treatments have been superseded by rituximab therapy. | 2C | JAPAN Guidelines 2023[7] |
| Remission period: After the patient has achieved full remission, corticosteroids should be discontinued at the earliest opportunity based on ADAMTS13 activity and inhibitor titer measurements. | Not graded | JAPAN Guidelines 2023[7] |
| Patients presenting for the first time with TTP in pregnancy should initially be treated as per iTTP with plasma exchange (PEX) and steroids. | 1A | British Guidelines 2023[10] |
| For pregnant women with iTTP refractory to PEX and steroids or who relapse, additional treatment options include ciclosporin, azathioprine and rituximab. | 2C | British Guidelines 2023[10] |
| In case of pregnant patients with iTTP and decreased plasma ADAMTS13 activity but with no clinical signs/symptoms, prophylactic treatment is recommended over no prophylactic treatment. | Strong recommendation, very low certainty evidence | ITSH 2020[11] |

| | | |
|---|---|---|
| For pregnancy associated TTP:<br>Steroids can be used until the results of ADAMTS13 antibodies are available. Rituximab has been used during pregnancy for a variety of autoimmune conditions but is reserved for severe or refractory immune mediated disease or when disease is life threatening and only after discussion with a consultant hematologist. | Not graded | NHS Guidelines 2022[6] |
| For pregnant women with cTTP, regular SD-FFP replacement therapy should be given prophylactically to prevent clinical TTP relapse. | 1B | British Guidelines 2023[10] |
| In case of cTTP in remission: either plasma infusion or a watch and wait strategy and no use of factor VIII concentrate but a watch and wait strategy | Conditional recommendation, very low certainty evidence | ITSH 2020[11] |
| In case of pregnant patients with cTTP, prophylactic treatment with plasma infusion is recommended over FVIII products for prophylaxis | Conditional recommendation, very low certainty evidence | ITSH 2020[11] |
| For congenital TTP:<br>Current treatment consists of use of Octaplas® infusions, or a virally inactivated intermediate purity factor VIII concentrate containing ADAMTS13 such as 8Y or virally inactivated FFP such as Octaplas®. Frequency of treatment is variable; some patients require regular prophylactic therapy to maintain normal platelet counts whereas more mildly affected phenotypes may only require occasional treatment. | Not graded | NHS Guidelines 2022[6] |
| Once platelet count has improved, clinicians use antithrombotic agents (i.e., aspirin and low-molecular-weight heparins). | Not graded | KSA and UAE Guidelines 2022[4] |

Major recommendations for suggested drug therapies are summarized in the table below:

**Table 2**. Summary of SFDA-Registered Drug Therapies

| Medication | Indication | Line of Therapy | Level of Evidence/ Recommendation | HTA Recommendations |
|---|---|---|---|---|
| **Prednisone, methylprednisolone, and dexamethasone** | In all confirmed TTP cases | **1st** | 1B[7] | N/A |
| **Caplacizumab** | In all confirmed TTP cases | **1st** | 1A[10] | Positive recommendation from NICE, IQWIG and HAS<br>Negative recommendations from PBAC and CADTH |
| **Mycophenolate mofetil** | Can be used in combination as first line therapy with corticosteroids in parallel to plasma exchange. Some small sized studies have examined its use in relapsed TTP who received multiple lines of treatment, however, a formal longer is warranted. | **1st** | Not graded[4] | N/A |
| **Rituximab** | In refractory and relapsed cases | **Subsequent** | 2B[7] | N/A |
| **Cyclosporine** | This drug is recommended as an alternative option for recurrent or refractory TTP | **Subsequent** | 2B[7] | N/A |

| | | | | |
|---|---|---|---|---|
| **Cyclophosphamide** | This drug is recommended as an alternative option in patients with refractory or relapsing TTP | **Subsequent** | 2B[7] | N/A |
| **Vincristine** | In relapsed/refractory patients with TTP | **Subsequent** | Not graded[4] | Moderate recommendation in iTTP resistant to usual treatments from HAS[12] |
| **Bortezomib** | In relapsed/refractory patients with TTP | **Subsequent** | Not graded[4] | N/A |
| **Azathioprine** | For patients and pregnant women with iTTP refractory to PEX and steroids or who relapse | **Subsequent** | 2C[10] | Positive recommendation from HAS |
| **Aspirin** | It is recommended once platelet count has improved, in all confirmed TTP cases, to prevent thrombosis. | **1st** | 2B[7] | N/A |
| **Enoxaparin** | It is recommended once platelet count has improved, in all confirmed TTP cases, to prevent thrombosis. | **1st** | 2B[7] | N/A |

The report concludes with the addition of a key recommendation synthesis section, which emphasizes the utilization of each drug class for specific patient groups.

# Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

## 1.1 KSA Guidelines

### 1.1.1 Approaches to Acquired Thrombotic Thrombocytopenic Purpura Management in Saudi Arabia (2022)

This **review article** published by AlHejazi et al. in the Journal of Applied Hematology in 2022 is a narrative based on available literature. The key discussions of the KSA experts and members of "Approaches to aTTP Management" Advisory Board meeting held in 2020 have been incorporated as expert opinions. The aim of the current review is to summarize the current knowledge regarding the epidemiology, pathophysiology, and management of aTTP, including newer therapies to provide a consensus and recommendations by the authors who are hematology experts in the Kingdom of Saudi Arabia (KSA) regarding aTTP Management[8].

The main recommendations are summarized below.

1. aTTP is a rare condition with diagnostic challenges, and early treatment is the key to better patient outcome. The panel **endorses the ISTH guidelines** on aTTP management to **start treatment based on the presumptive diagnosis** and continue treatment until remission or aTTP is ruled out and an alternate diagnosis is established.
2. Given the proven efficacy of caplacizumab in the TITAN and HERCULES trial, the use of **caplacizumab in addition to TPE and immunosuppression** is recommended in **confirmed** aTTP episodes. A national consensus be drawn to guide the physicians on the diagnosis and treatment of aTTP incorporating the newer treatment modalities, curated for the patient population of the KSA.
3. Long-term follow-up studies and real-world evidence should be gathered to generate evidence on the efficacy of caplacizumab in mitigating long-term morbidity and improving the health-related quality of life.

### 1.1.2 Burden of Acquired Thrombotic Thrombocytopenic Purpura: KSA and UAE Expert Consensus for Improved Disease Management (2022)

The primary focus of this **study** was to establish the epidemiology of aTTP, the current clinical practice, and unmet needs and to develop local consensus statements on aTTP management in KSA and UAE. Cost of the disease and socioeconomic burden were a secondary focus.

Hematologists from KSA and UAE with clinical experience of aTTP took modules via online surveys on burden, management, and clinical economics of aTTP. This was followed by a live group session, participated by hematologists, where they agreed on their inputs of the consensus statements for each country. The main findings related to the management of aTTP in KSA are detailed below[4]. Findings for UAE were not included.

**Diagnosis**

- ADAMTS13 activity testing is preferred for diagnosis; however, currently, there are challenges with access to this test.
    - ADAMTS13 testing is not readily available in KSA, and samples are sent abroad for testing with results taking up to 2 weeks. In the absence of ADAMTS13 testing, complete blood count and lactate dehydrogenase are used at diagnosis, after 2–3 weeks of treatment initiation and 2–3 months after treatment.

**Treatment**

- Plasma exchange and immunosuppressants (such as corticosteroids and rituximab, used commonly off-label) are key elements in aTTP treatment.
- Plasma infusion is used temporarily if plasma exchange is not immediately available.
- Once platelet count has improved, clinicians use antithrombotic agents (i.e., aspirin and low-molecular-weight heparins).
- Packed red blood cells are used to correct for hemolytic anemia, if necessary.
- Fresh frozen plasma or cryodepleted plasma are used for plasma exchange. Until plasma exchange can be initiated, plasma infusion (15–30 ml/kg of body weight, daily) is used. In parallel, corticosteroids (e.g., prednisone) should be used for all patients, bortezomib in refractory patients, and vincristine in relapsed/ refractory patients.

The treatment algorithm for the management of TTP in KSA (including diagnosis) is shown in figure 1.

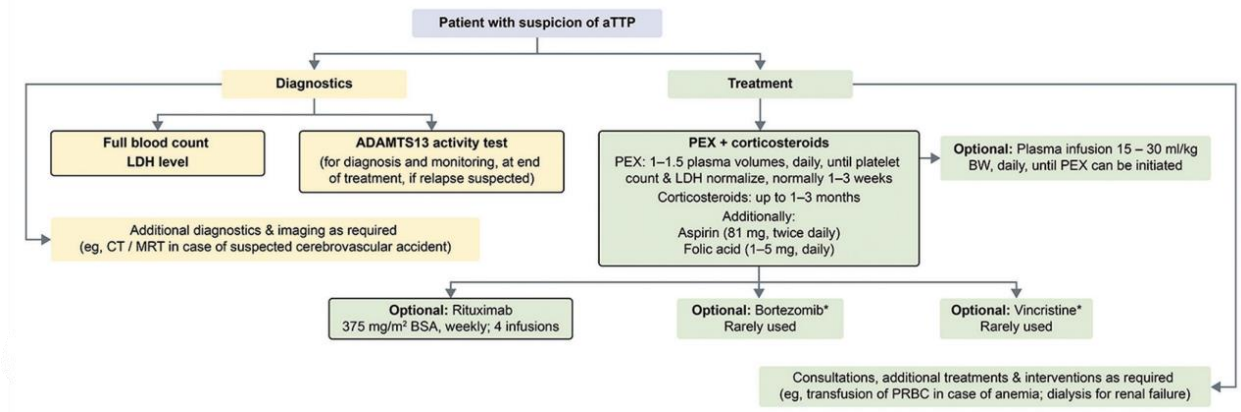


***Figure 1.*** *Treatment Algorithm for the Management of Acquired Thrombotic Thrombocytopenic Purpura (aTTP) in the Kingdom of Saudi Arabia (KSA). Retrieved from Journal of Applied Hematology. 2022;13(3):145.*

## 1.2 European Guidelines

### 1.2.1 A British Society for Haematology Guideline: Diagnosis and Management of Thrombotic Thrombocytopenic Purpura and Thrombotic Microangiopathies (2023)

The British Society for Haematology published its 2023 clinical guidelines with the aim of providing guidance on the management of TTP sand related thrombotic microangiopathies (TMAs)[10].

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations.

The major recommendations are listed below.

**Diagnosis of TTP**

- The initial diagnosis of TTP and treatment decisions should be made on clinical history, examination and laboratory testing including blood film. (1A)
- Pretreatment samples should be obtained to measure ADAMTS13 activity levels and to detect anti-ADAMTS13 antibodies. (1A)
- The early measurement of ADAMTS13 activity is recommended over using scoring systems. (2C)
- Serological tests for HIV, HBV and HCV, autoantibody screen and when appropriate, a pregnancy test, should be performed at presentation. (1A)

- A low ADAMTS13 activity level based on a fully automated assay/semi-quantitative assay may require confirmation (by a FRETS-based assay) depending on the index of clinical suspicion for TTP. (2C)

**Treatment of acute TTP**

Initial management

- TTP is a medical emergency requiring time-critical transfer to a dedicated treatment centre. (1A)
- Pretransfer review should be undertaken by an appropriately skilled medical team. Intubation should be considered for clinically unstable patients. (1B)
- From referral of a suspected diagnosis of TTP and transfer, PEX should be initiated within four to eight hours. (1A)
- Platelet transfusion should be avoided. (1B)

Therapies for use in TTP

- Caplacizumab should be initiated on confirmation of acute iTTP and for up to 30 days following completion of PEX. In patients who remain severely ADAMTS13 deficient (<20 IU/dL) caplacizumab therapy may be continued. (1A)
- Intravenous daily methylprednisolone (e.g. 1 g/day for three consecutive days—adult dose) or high-dose oral prednisolone (e.g. 1 mg/kg/day) should be considered, with tapering when there is a sustained increase in ADAMTS 13 activity levels. (1B)
- PEX, with OctaplasLG should be started with 1.5 PV exchanges, and reassessed daily, reducing to 1.0 V when the clinical picture and laboratory tests are stabilising. (1A)
- Intensification in frequency and or volume of PEX procedures should be considered in life-threatening cases. (1B)
- Daily PEX should stop when the platelet count is sustained >150 × $10^9$/L. (2B)
- Monoclonal anti-CD20 therapy should be initiated within 3 days of acute iTTP admission. (1B)
- In patients who have refractory iTTP or have severe ADAMTS13 deficiency despite anti-CD20 therapy, alternative immunosuppressive therapy should be considered. (2B)
- Alternate immunomodulatory therapies, such as azathioprine, cyclophosphamide, splenectomy may be alternative options in patients with refractory or relapsing iTTP. (2C)

- All hospitalized/immobilized patients should receive thromboprophylaxis once platelet counts are ≥50 × 109/L, even when treated with caplacizumab. (1B)

**Medical follow-up**

- Patients should have lifelong follow-up including ADAMTS13 assay monitoring. (1B)
- Neurocognitive assessment and psychology support for anxiety/depression should be offered. (1C)
- Pre-emptive therapy with Rituximab should be given when ADAMTS13 activity <20 IU/dL or higher levels associated with clinical symptoms. (1B)

**Congenital TTP (cTTP)**

- cTTP should be considered in severe neonatal jaundice with thrombocytopenia and in children with unexplained thrombocytopenia. (1B)
- Siblings of confirmed cTTP cases should be screened, including ADAMTS13 activity and genetic analysis. (1C)
- The diagnosis of congenital TTP is confirmed by ADAMTS13 activity <10 IU/dL, no anti-ADAMTS13 antibody and confirmation of homozygous or compound heterozygous variants in the ADAMTS13 gene. (1B)
- For an acute cTTP episode, solvent detergent plasma infusion is recommended. Intermediate purity factor VIII (e.g. BPL8Y) can be considered. (1B)
- ADAMTS13 prophylaxis should be considered for all patients with cTTP, with an individualized approach to dose and frequency according to symptoms, whether overt or non-overt. (1B)

**Pregnancy-associated TTP**

- Patients presenting for the first time with TTP in pregnancy should initially be treated as per iTTP with PEX and steroids. (1A)
- Women presenting with TTP in pregnancy should have investigations to determine whether they have iTTP or a first presentation of cTTP. (1B)
- For pregnant women with iTTP refractory to PEX and steroids or who relapse, additional treatment options include ciclosporin, azathioprine and rituximab. (2C)
- For pregnant women with cTTP, regular SD-FFP replacement therapy should be given prophylactically to prevent clinical TTP relapse. (1B)

- For women with iTTP, normalization of ADAMTS13 activity prior to pregnancy is recommended. (1B)

**HIV-associated TTP**

- HIV-associated iTTP should be treated with HAART and plasma exchange/steroids/caplacizumab. (1B)
- In patients with low/undetectable viral load, ADAMTS13 relapse or clinical relapse should be treated as standard iTTP. (1C)

**Co-existing autoimmune conditions**

- PEX is not recommended for cancer or transplant-associated TMA (thrombotic microangiopathies). (1C)
- Pancreatitis-associated TMA is not associated with a severely reduced ADAMTS13 activity and the benefit of PEX is unclear. (2C)

**Hemolytic uremic syndrome (HUS)**

- In TMAs associated with renal impairment, ADAMTS13 activity should be checked to exclude TTP. (1B)
- CM HUS (complement-mediated hemolytic uremic syndrome) is a clinical diagnosis (that can sometimes be confirmed by detection of a pathogenic complement gene variant or relevant autoantibody) for which prompt complement inhibitor therapy should be initiated. (1A)

### 1.2.2 International Society on Thrombosis and Haemostasis (ISTH) Guidelines for the Treatment of Thrombotic Thrombocytopenic Purpura (2020)

The ISTH published clinical practice guidelines for the diagnosis and treatment of TTP in 2020[11]. The guidelines recommendations are summarized in table 3.

The strength of a recommendation is expressed as either strong ("the guidelines panel recommends…") or conditional ("the guidelines panel suggests…").

A strong recommendation means that the panel is confident that the desirable effects of following the recommendation outweigh the undesirable effects. Strong recommendations are usually based on high-quality evidence in which we have high confidence. However, in certain paradigmatic situations, strong recommendations are issued in the absence of high certainty evidence; in these instances, the reasoning behind the panel's decision is clearly laid out.

A conditional recommendation means that the panel believes that the desirable effects of following the recommendation probably outweigh the undesirable effects.

In 2022, the ISTH guidelines were evaluated and endorsed by the European Renal Best Practice Working Group (ERBP)[13].

**Table 3.** Summary of the ISTH 2020 Guidelines Recommendations

| Recommendation setting | Intervention | Strength |
|---|---|---|
| Access to ADAMTS13 testing and patients with a high clinical suspicion of iTTP (High clinical suspicion of TTP: ≥90% pretest probability of iTTP based on clinical assessment or a formal clinical risk assessment method such as PLASMIC score or French score) | **Step 1:** Plasma sample for ADAMTS13 testing before an initiation of TPE or use of any blood product.<br>**Step 2:** TPE and corticosteroids without waiting for the results of ADAMTS13 testing.<br>**Step 3:** Consider early administration of caplacizumab before receiving plasma ADAMTS13 activity results.<br>**Step 4:**<br>• If ADAMTS13 test is positive (Positive result: ADAMST13 activity <10 IU/dL (or <10% of normal): continue caplacizumab.<br>• If ADAMTS13 test is negative (Negative result: ADAMTS13 activity >20 IU/dL (or >20% of normal): stop caplacizumab and consider other diagnoses.<br>**Step 5:** For patients with a positive ADAMTS13 inhibitor testing, also consider adding rituximab as early as possible, as most of these adult patients (>95%) have autoantibodies against ADAMTS13. | Conditional recommendation, low certainty evidence |
| Access to ADAMTS13 testing and patients with intermediate or low clinical suspicion of iTTP (Intermediate or low clinical suspicion: based | **Step 1:** Plasma sample for ADAMTS13 testing before an initiation of TPE or use of any blood product.<br>**Step 2:** Consider starting TPE and corticosteroids, depending on the clinician's judgment and assessment of the individual patient.<br>**Step 3:** No caplacizumab until the result of plasma ADAMTS13 activity is available. | Conditional recommendation, low certainty evidence |

| | | |
|---|---|---|
| on clinical assessment or a formal clinical risk assessment method such as PLASMIC score or French score) | **Step 4:**<br>• If ADAMTS13 test is positive: consider adding caplacizumab and rituximab.<br>• If ADAMTS13 test is negative: do not start caplacizumab and consider other diagnoses. | |
| No access to plasma ADAMTS13 | No caplacizumab regardless of the pretest probability of TTP. | Conditional recommendation, low certainty evidence |
| iTTP, first acute event | Addition of corticosteroids to TPE over TPE alone. | Strong recommendation, very low certainty evidence |
| iTTP, first acute event | Addition of rituximab to corticosteroids and TPE over corticosteroids and TPE alone. | Conditional recommendation, very low certainty evidence |
| Relapse of iTTP | Addition of corticosteroids to TPE over TPE alone. | Strong recommendation, very low certainty evidence |
| Relapse of iTTP | Addition of rituximab to corticosteroids and TPE over corticosteroids and TPE alone. | Conditional recommendation, very low certainty evidence |
| Acute event of iTTP (first event or relapse) | Use of caplacizumab over non-use of caplacizumab. | Conditional recommendation, moderate certainty evidence |
| iTTP in remission, but low plasma ADAMTS13 activity and no clinical signs/symptoms | Use of rituximab over non-use of rituximab for prophylaxis. | Conditional recommendation, very low certainty evidence |
| cTTP in remission | Either plasma infusion or a watch and wait strategy. | Conditional recommendation, |

| | | |
|---|---|---|
| | | very low certainty evidence |
| cTTP in remission | No use of factor VIII concentrate but a watch and wait strategy. | Conditional recommendation, very low certainty evidence |
| Pregnant patients with iTTP and decreased plasma ADAMTS13 activity but with no clinical signs/symptoms | Prophylactic treatment over no prophylactic treatment. | Strong recommendation, very low certainty evidence |
| Pregnant patients with cTTP | Prophylactic treatment over no prophylactic treatment. | Strong recommendation, very low certainty evidence |
| Pregnant patients with cTTP | Prophylactic treatment with plasma infusion over FVIII products for prophylaxis. | Conditional recommendation, very low certainty evidence |

### 1.2.3 NHS Guideline for the Management of Adult Patients with a Suspected Diagnosis of Thrombotic Thrombocytopenic Purpura (2022)

The guidelines recommend the following[6]:

- Therapeutic plasma exchange (PEX):
    - Daily plasma exchange is the mainstay of treatment for TTP. PEX should be started within 4 hours of admission and within of 8 hours of initial diagnosis.
    - Delays in treatment have been shown to increase treatment failure and is associated with worse prognosis.
    - The UK Department of Health recommends the use of solvent/detergent-treated (S/D) plasma in TTP patients – this is OctaplasLG® at UHL.
    - If there is a delay in commencing PEX, plasma infusion of 15ml/kg OctaplasLG® should be administered. Plasma infusion is inferior to PEX so every effort should be made to commence PEX as soon as possible.

- In cases of severe disease (hemodynamically or neurologically unstable or new symptoms despite PEX) or sudden deterioration, consideration should be given to twice daily exchange. The optimum duration of PEX is unknown but consensus recommends that daily PEX should continue for a minimum of 2 days after complete remission, defined as a normal platelet count >150 x109/l.
- Tapering (reducing frequency and/or volume of PEX) has not been shown to reduce relapse rates and therefore is not recommended.
- PEX should be started daily with 1.5 the predicted plasma volume of the patient (PV) using OctaplasLG®. The patient should be reviewed daily, and the volume of exchange decided by the attending consultant. The volume of exchange can be reduced to 1·0 PV when the clinical condition and laboratory test results are stabilizing.

- Steroid therapy:
  - All patients should receive adjuvant corticosteroid therapy.
  - Unless contraindicated, this should initially be pulsed methylprednisolone 1g IV daily for the first 3 days.
  - All doses should be given immediately after PEX. A longer duration of steroids may be needed, and this can usually be given orally but this will be decided following discussion with the consultant hematologist.
- Transfusion:
  - Platelet Transfusions are contraindicated in TTP - unless the patient has life-threatening hemorrhage. Platelet transfusion must not be given without prior discussion with a consultant hematologist.
  - Red cell transfusion should be administered according to clinical need. Patients with microangiopathy can decrease their Hb levels rapidly due to hemolysis which may occur suddenly. PEX can also reduce Hb levels. It is important that the transfusion laboratory.
- Caplacizumab:
  - It has been shown to improve time to platelet normalization, significantly reduce exacerbations of TTP, more rapidly improve end organ biomarkers and reduce time in ICU and overall hospital stay.
  - Caplacizumab is approved by NICE for use in patients with:
    - Acute acquired, immune TTP (with confirmed ADAMTS13 deficiency)
    - Age more than 12 years

        - Weight more than 40kg.
    - Caplacizumab treatment should only be initiated by a non-malignant hematology consultant.
    - The differential diagnosis of TMA is wide. The use of caplacizumab for TMA other than TTP may be associated with organ related bleeding, particularly if there is severe thrombocytopenia and use is not recommended. Consideration should be given to whether the TTP is congenital because Caplacizumab should not be given in cases of congenital TTP.
    - Aspirin, other antiplatelet drugs and LMWH should not routinely be given during caplacizumab treatment.
    - Dosing regimen of caplacizumab:
        - An initial IV bolus of 10mg should be given before plasma exchange
        - A further 10mg SC should be given after plasma exchange
        - A 10mg SC should be continued once daily, given after plasma exchange for the duration of plasma exchange and at least 30 days afterward
        - Caplacizumab may require continuation for longer for patients with ongoing low ADAMTS 13 levels
        - The exact duration of treatment will be determined by the non-malignant hematology consultant, once improvement in ADAMTS13 activity has been demonstrated
    - Bleeding whilst receiving caplacizumab:
        - The drug must be withheld, in discussion with the hematology consultant
- Rituximab:
    - Rituximab (Anti CD-20 monoclonal antibody) has been shown to be safe and effective in immune TTP with reduced time to remission in relapsed/refractory TTP as well as reducing the risk of relapse. A decision to give Rituximab should only be made in discussion with a Consultant Hematologist.
    - The dose of rituximab is 375mg/m2 IV given once every 3-4 days for a total of 4 doses. PEX should be withheld for at least 4 hours after completion of rituximab. All patients should receive pre-medication

with Chlorphenamine 10mg IV and paracetamol. Consent for treatment should be taken if the patient has capacity.

- Exclusion criteria for Rituximab
  - Women who are known to be pregnant or breast feeding
  - Both male and female patients receiving Rituximab should ensure adequate contraception for 12 months following treatment.
  - Patients who are HIV positive. (This group of patients may not benefit from Rituximab. HIV positive status is also a relative contraindication for Rituximab).
  - Patients with hemolytic- uremic syndrome which is not associated with reduced ADAMTS13 levels.
  - Patients in whom TTP is secondary to transplantation.
  - Some patients with drug-associated TTP (individualized patient discussion will be required)
  - Active malignancy
  - Patients with evidence of prior Hep B infection should be offered prophylaxis

- Supportive measures:
  - Folic acid 5mg OD in all patients and continue on discharge
  - All patients should receive a proton pump inhibitor for the duration that they remain on corticosteroids.
  - Fever is one of the defining features of TTP - the patient should be investigated for underlying infection; occult infection may prevent response to plasma exchange or precipitate relapse. Antibiotics should be prescribed if there is suspicion of infection or if the patient is hypotensive.
  - Hepatitis B vaccination should be offered to all patients once platelet count >50 $x10^9$/l
  - Thromboembolism is a recognized complication during rapid platelet recovery; all patients should wear graduated compression stockings from admission to discharge.
  - If the patient has NOT received caplacizumab for any reason:
    - Aspirin 75mg OD should be commenced when platelet count >50 $x10^9$/l

        - Low molecular weight heparin prophylaxis (Dalteparin) should be commenced when platelet count >50 x$10^9$/l
    - For patients who have received caplacizumab, Aspirin 75mg OD can be started once caplacizumab treatment has been stopped.

- Congenital TTP:
    - Current treatment consists of use of Octaplas infusions, or a virally inactivated intermediate purity factor VIII concentrate containing ADAMTS13 such as 8Y or virally inactivated FFP such as Octaplas. Frequency of treatment is variable; some patients require regular prophylactic therapy to maintain normal platelet counts whereas more mildly affected phenotypes may only require occasional treatment.
- Pregnancy associated TTP:
    - If TTP is suspected during pregnancy, the patient should be managed as per the standard TTP protocol with direct admission to AICU. The Obstetric Haematology team should be informed at the earliest opportunity. The mainstay of treatment of acute TTP in pregnancy is PEX (or plasma infusion if there is a delay in accessing PEX).
    - Steroids can be used until the results of ADAMTS13 antibodies are available. Rituximab has been used during pregnancy for a variety of autoimmune conditions but is reserved for severe or refractory immune mediated disease or when disease is life threatening and only after discussion with a consultant hematologist.
    - Caplacizumab is not licensed for use in pregnancy and there is no clinical experience in this setting. Caplacizumab should therefore not be used in pregnant patients.
    - When the platelet count is >50 x $10^9$/l, aspirin 75mg and dalteparin prophylactic dose (weight based as per UHL policy) should be started.
    - Subsequent treatment will depend on the gestation at presentation but PEX is likely to be needed regularly until delivery and in the postpartum period. It should be noted that delivery does not guarantee remission of TTP. For patients with immune TTP, frequency of PEX will guided by platelet counts and ADAMTS13 antibody levels. These patients should be followed up on discharge initially in the obstetric hematology clinic.
    - Women who have had TTP are at risk of relapse during any subsequent pregnancy. They also have a higher risk for pregnancy-related complications. These women should be referred to the combined obstetric hematology clinic for pre-pregnancy counselling. Women of

child-bearing age should use adequate contraception other than the estrogen containing oral contraceptive pill for the first 12 months after receiving Rituximab.

- Refractory TTP:
    - Refractory disease is defined as progression of clinical symptoms or persistent thrombocytopenia despite PEX. Management of these patients should be individualized and always in discussion with a consultant hematologist.

## 1.4 International Guidelines

### 1.4.1 Diagnostic and Treatment Guidelines for Thrombotic Thrombocytopenic Purpura (TTP) in Japan (2023)

In 2017, the expert physicians who were members of the TTP group of the Blood Coagulation Abnormalities team in the Japanese government-funded Health, Labor, and Welfare Scientific Research Grant Project published their consensus report entitled "Diagnostic and Treatment Guidelines for TTP 2017". Given the improvements in the national health insurance policy for TTP, the original guidelines were partially revised and published as the "Diagnostic and Treatment Guidelines for TTP 2020". The present article published in 2023 is an update to the 2020 guidelines[7].

The guidelines recommendations are accompanied by a grading scheme, outlined as follows:

**Table 4.** Japan 2023 Levels of Recommendations Based on the GRADE System

| **Strength of Recommendation** | |
|---|---|
| **1. Strong** | Benefits clearly outweigh risks and burden (or vice versa) in most patients |
| **2. Weak** | Benefits are closely balanced with risks and burden |
| **Quality of Supporting Evidence** | |
| **A** | Evidence established from multiple RCTs or very strong evidence from observational studies |
| **B** | Limited evidence from RCTs or strong evidence from observational studies |
| **C** | Evidence from RCTs with serious flaws or weak or indirect evidence from observational studies |

The main recommendations from the 2023 guidelines are detailed below.

## I. Immune-mediated TTP

### a. Acute phase

**Plasma exchange (grade of recommendation: 1A)**

- Plasma exchange with fresh frozen plasma (FFP) (50-75 mL/kg) should be given once daily. The FFP volume is 1.0–1.5 times the patient's circulating plasma volume.
- It should be continued until 2 days after the platelet count is normalized (≥ 150 × 109/L).
- Human serum albumin solutions are not recommended for replacement, because these do not supplement ADAMTS13 like FFP.
- FFP infusion may be performed in emergency cases. An analysis of response and survival showed that plasma exchange is superior to plasma infusion in the treatment of TTP.

**Corticosteroid therapy (grade of recommendation: 1B)**

- Corticosteroids are administered either as pulse or high-dose therapy (no consensus regarding the superiority of either modality). Both modalities are used as off-label in Japan.
- Lower doses should be considered in patients who are elderly or have diabetes mellitus or severe infections.
- Pulse corticosteroid therapy with Methylprednisolone 1000 mg:
    - After receiving plasma exchange, this dose is given over 2 hours by drip infusion.
    - The dose should be tapered after administration for 3 consecutive days. The dose-reduction regimen is made with reference to the platelet count and ADAMTS13 test results.
    - If the physician wishes to extend methylprednisolone therapy for the treatment of neurologic symptoms, or under conditions of intensive care unit (ICU) management, the corticosteroid may be given at 500, 250, and 125 mg/day, with each dosage administered for 2 days and in this order. The dosage regimen should then be switched to oral corticosteroids 30 mg/ day, and subsequently tapered.

    - If the physician decides to switch to oral therapy after the first 3 days of drip infusion, oral prednisolone 0.5–1.0 mg/kg/day should be administered, and the dosage tapered.
- High dose corticosteroid therapy with oral prednisolone 1 mg/kg/day:
    - Prednisolone dosage should be tapered with reference to the platelet count and ADAMTS13 test results.
    - The initial dosage (1 mg/kg/day) is maintained for 2 weeks, followed by a rapid reduction to 0.5 mg/kg/day. The weekly dose should further be reduced by approximately 2.5–5.0 mg each week, taking note of the platelet count and ADAMTS13 inhibition test results.

**Caplacizumab (grade of recommendation: 1A)**

- Caplacizumab, a single-chain humanized monoclonal antibody against the A1 domain of human VWF, was approved in September 2022 for marketing in Japan. notably, this was the first time that this mortality was reduced by a modality other than plasma exchange.
- On the first day, a 10-mg dose is administered intravenously at least 15 min before the start of plasma exchange, and another 10-mg dose is administered subcutaneously after the end of the plasma exchange session.
- On subsequent days, a 10-mg dose is administered subcutaneously after each daily plasma exchange. After termination of the plasma exchange therapy, once-daily 10-mg doses are administered subcutaneously for 30 days.
- If ADAMTS13 activity remains < 10% after the 30-day regimen, caplacizumab may be continued for an additional 28 days.
- Although caplacizumab therapy may be started before a marked decrease in ADAMTS13 activity is confirmed, it should be discontinued immediately if ADAMTS13 activity is found to be ≥ 10% and TTP is ruled out.

**Rituximab (grade of recommendation: 2B)**

- In Japan, rituximab is indicated for refractory or recurrent TTP only, and its use in the acute phase of TTP is not subject to national health insurance coverage. However, physicians may consider rituximab for the treatment of patients in the acute phase of iTTP
- The recommended rituximab therapy regimen is once weekly for 4 weeks.
- Rituximab 375 mg/m2 + premedication with antihistaminic drugs and acetaminophen should be administered, due to the side effects of the drug. An infusion pump should be employed to increase the infusion rate gradually.

- In patients undergoing plasma exchange, rituximab should be administered after the end of the plasma exchange session.

**Antiplatelet drugs (grade of recommendation: 2B)**

- Oral aspirin may be administered at 81–100 mg once daily in the morning until corticosteroids are terminated.
- Low-dose aspirin is empirically administered in patients whose platelet count has returned to > 50 × 109/ L, although its impact on preventing TTP relapse has not been substantiated.
- Concomitant use of aspirin and caplacizumab may increase the risk of bleeding and should be avoided.
- Given that iTTP developed in association with ticlopidine and clopidogrel, these drugs should be avoided in patients with TTP.

**Other treatments**

- Patients without cardiac disorders may undergo red blood cell transfusion if hemoglobin levels decrease to < 7.0 g/dL (grade of recommendation: 1A).
- In patients with cardiac disorders, hemoglobin levels < 8.0 g/dL may suggest the need for red blood cell transfusion.
- Platelet transfusion is indicated for patients with life-threatening bleeding. Prophylactic platelet transfusion in other situations, however, is contraindicated as it may aggravate thrombosis (grade of recommendation: 1B).
- In patients manifesting iTTP secondary to the use of a specific drug, the drug should be immediately discontinued.
- If the patient has an underlying condition, only the drugs to treat the condition should be continued.
- Since ADAMTS-13 activity levels may be severely lowered in patients with secondary iTTP, plasma exchange in these patients should be conducted using a similar protocol as that used in patients with primary TTP.

### b. Refractory or early-relapse TTP

- If the platelet count does not increase to 50 × $10^9$/ L after five plasma exchange sessions, or if the platelet count decreases to < 50 × $10^9$/L after initially recovering to > 150 × $10^9$/L, the physician should consider **rituximab in combination with plasma exchange** (grade of recommendation: 1B).

- Rituximab (grade of recommendation: 1B) for the treatment of recurrent or refractory TTP: Rituximab takes 10–14 days to demonstrate a clinical impact, and plasma exchange should often be conducted in the interim
- **Other treatments for the treatment of recurrent or refractory TTP:**
    - **Cyclophosphamide (off-label use in Japan, grade of recommendation: 2B):**
        - Cyclophosphamide 500 mg/m2 administered once daily over 2 hours
        - This regimen is restricted to a single dose, as multiple doses may cause bone marrow suppression.
    - Vincristine (off-label use in Japan, grade of recommendation: 2B):
        - Vincristine 1 mg/m2 is administered IV once daily at a slow infusion rate.
        - This regimen is restricted to a single dose, as multiple doses may cause neurotoxicity and bone marrow suppression.
    - Cyclosporine (off-label use in Japan, grade of recommendation: 2B)
        - Oral cyclosporine 4 mg/kg/day is administered in two divided doses.
        - Blood levels of cyclosporine should be monitored to maintain a trough level of approximately 100–200 ng/mL.
    - Splenectomy surgery (grade of recommendation: 2C) and high-dose immunoglobulin (grade of recommendation: 2C) were frequently administered to treat patients with refractory or recurrent TTP. These treatments have been superseded by rituximab therapy.

**c. Remission period**

- After the patient has achieved full remission, corticosteroids should be discontinued at the earliest opportunity based on ADAMTS13 activity and inhibitor titer measurements.
- No effective prophylactic treatments have been recommended for patients in remission.
- To minimize the risk of relapse, patients should follow up with the physician regularly during the first several years after achieving remission and undergo monitoring of the platelet count and ADAMTS13 activity.
- In remitted patients with normal platelet counts, ADAMTS13 activity may be severely reduced and ADAMTS13 inhibitors may be present. Patients whose

ADAMTS13 activity is significantly reduced (ADAMTS13 relapse) or who are positive for ADAMTS13 inhibitors are at high risk of clinical relapse. The preemptive use of rituximab is a viable option.

- If patients in remission of iTTP show an ADAMTS13 activity decrease to < 10%, rituximab may be considered for preventing relapse. (off-label use in Japan, grade of recommendation: 2B).

### II. Congenital TTP

**FFP transfusion (grade of recommendation: 1B)**

- FFP volume of 5–10 mL/kg is empirically transfused once every 2–3 weeks.
- At the time of onset, the physician should transfuse FFP at a volume of 10 mL/kg and monitor the clinical impact.
- To minimize the risks of allergy, anaphylaxis, disease transmission, and other adverse reactions to FFP infusion, efforts should be made to collect FFP from the smallest possible number of donors.
- Antihistamines and corticosteroids may sometimes be used to prevent allergic reactions to FFP, but there is a paucity of scientific evidence to support these treatments.
- Currently, the amount of FFP necessary to prevent organ damage on a long-term basis is unknown.

## 1.5 Systematic Reviews & Meta Analyses

Table 5 tackles a systematic review and meta-analysis issued in **2022** for **Thrombotic Thrombocytopenic Purpura.**

**Table 5.** TTP Systematic Reviews and Meta Analyses

| Study title | Author (year) | Primary Objective | Outcomes | Results |
|---|---|---|---|---|
| Adding caplacizumab to standard of care in thrombotic thrombocytopenic purpura: a systematic review and meta-analysis | Djulbegovic et al. (2022)[9] | Concerns about RCT selection bias and the high cost of caplacizumab warrant examination | The **primary efficacy and safety outcomes** were all-cause mortality and | Compared with SOC, caplacizumab was associated with a nonsignificant reduction in the relative risk [RR] of death in RCTs (RR, 0.21; 95% confidence interval [CI], 0.05-1.74) and observational |

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| | | of all evidence, including realworld observational studies. In this systematic review and meta-analysis, the authors searched for comparative studies evaluating standard of care (SOC) with or without caplacizumab for the treatment of iTTP. Consequently, the authors assessed risk of bias using the Cochrane risk-of-bias-2 tool (RCTs) and the Newcastle Ottawa Scale (observational studies). | treatment-emergent bleeding, respectively. **Secondary outcomes** included exacerbation and relapse, refractory iTTP, and time to response | studies (RR, 0.62; 95% CI, 0.07-4.41).<br>Compared with SOC, caplacizumab was associated with an increased bleeding risk inRCTs (RR, 1.37; 95%CI, 1.06-1.77).<br>Inobservational studies, bleeding risk was not significantly increased (RR, 7.10; 95% CI, 0.90-56.14).<br>Addition of Caplacizumab was associated with a significant reduction in refractory iTTP and exacerbation risks and shortened response time but increased relapse risk.<br><br>**Conclusion**:<br>Frontline addition of caplacizumab does not significantly reduce all-cause mortality compared with SOC alone, although it reduces refractory disease risk, shortens time to response, and improves exacerbation rates at the expense of increased relapse and bleeding risk. |

# Section 2.0 Drug Therapy

## 2.1 Monoclonal Antibodies

### 2.1.1 Anti-von Willebrand Factor (vWF): Caplacizumab

Information on Caplacizumab is detailed in the table below[14]:

**Table 6.** Caplacizumab Drug Information

| **SCIENTIFIC NAME**<br>**Caplacizumab** | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA** | Yes |
| **US FDA** | Yes |
| **EMA** | Yes |
| **MHRA** | Yes |
| **PMDA** | Yes |
| **Indication (ICD-10)** | M31.1 |
| **Drug Class** | Monoclonal Antibody |
| **Drug Sub-class** | Anti-von Willebrand Factor (vWF) Monoclonal Antibody |
| **ATC Code** | B01AX07 |
| **Pharmacological Class (ASHP)** | Antithrombotic Agents, Misc |
| **DRUG INFORMATION** | |
| **Dosage Form** | Powder and solvent for solution for injection |
| **Route of Administration** | IV Use, SQ Use |
| **Dose (Adult) [DDD]*** | • An initial IV bolus of 10mg should be given at least 15 minutes before plasma exchange<br>• A further 10mg SC should be given after the end of the plasma exchange session<br>• A 10mg SC should be continued once daily, given after plasma exchange for the duration of plasma exchange and at least 30 days afterward |

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| | • Caplacizumab may require continuation for longer for patients with ongoing low ADAMTS 13 levels<br>• The exact duration of treatment will be determined by the non-malignant hematology consultant, once improvement in ADAMTS13 activity has been demonstrated<br>• If ADAMTS13 activity remains < 10% after the 30-day regimen, caplacizumab may be continued for an additional 28 days. |
| **Maximum Daily Dose Adults*** | N/A |
| **Dose (pediatrics)** | N/A |
| **Maximum Daily Dose Pediatrics*** | N/A |
| **Adjustment** | **Older Adult**<br>Refer to adult dosing.<br>**Altered Kidney Function: Adult**<br>There are no dosage adjustments provided in the manufacturer's labeling. However, no clinically meaningful effect was noted in caplacizumab pharmacokinetics in patients with CrCl 15 to 90 mL/minute.<br>**Hepatic Impairment: Adult**<br>There are no dosage adjustments provided in the manufacturer's labeling (has not been studied). Use with caution in patients with severe acute or chronic hepatic impairment; monitor closely for bleeding.<br>**Adjustment for Toxicity: Adult**<br>Bleeding: If clinically significant bleeding occurs, interrupt treatment. If rapid correction of hemostasis is required, von Willebrand factor concentrate may be administered. Monitor closely if caplacizumab is reinitiated. |
| **Prescribing edits*** | MD, PA, PE, AGE, CU |

| | |
|---|---|
| **AGE (Age Edit):** | It is approved for patients aged more than 12 years, according to NICE |
| **CU (Concurrent Use Edit):** | The guidelines recommend the use of caplacizumab in addition to TPE and immunosuppression (e.g., steroids) in confirmed aTTP episodes. |
| **G (Gender Edit):** | N/A |
| **MD (Physician Specialty Edit):** | Caplacizumab treatment should only be initiated by a non-malignant hematology consultant |
| **PA (Prior Authorization):** | Caplacizumab should be given to patients with confirmed aTTP (through ADAMTS13 testing), in patients aged 12 years or older who weigh at least 40 kg. It has a specific dosage regimen: An initial IV bolus of 10mg should be given at least 15 minutes before plasma exchange. A further 10mg SC should be given after the end of the plasma exchange session. A 10mg SC should be continued once daily, given after plasma exchange for the duration of plasma exchange and at least 30 days afterward. Caplacizumab may require continuation for longer for patients with ongoing low ADAMTS 13 levels. The exact duration of treatment will be determined by the non-malignant hematology consultant once improvement in ADAMTS13 activity has been demonstrated. If ADAMTS13 activity remains < 10% after the 30-day regimen, caplacizumab may be continued for an additional 28 days. It is to be given in addition to TPE and immunosuppression (e.g., steroids) by a non-malignant hematology consultant. |
| **QL (Quantity Limit):** | N/A |
| **ST (Step Therapy):** | N/A |
| **EU (Emergency Use Only):** | N/A |

| | |
|---|---|
| **PE (Protocol Edit):** | **It has a specific dosage regimen for patients aged 12 years and over who weigh at least 40 kg**: An initial IV bolus of 10mg should be given at least 15 minutes before plasma exchange. A further 10mg SC should be given after the end of the plasma exchange session. A 10mg SC should be continued once daily, given after plasma exchange for the duration of plasma exchange and at least 30 days afterward. Caplacizumab may require continuation for longer for patients with ongoing low ADAMTS 13 levels. The exact duration of treatment will be determined by the non-malignant hematology consultant once improvement in ADAMTS13 activity has been demonstrated. If ADAMTS13 activity remains < 10% after the 30-day regimen, caplacizumab may be continued for an additional 28 days. |
| **SAFETY** | |
| **Main Adverse Drug Reactions (most common and most serious)** | **Most common (frequency: >10%)**<br>Dermatologic: Urticaria<br>Gastrointestinal: Gingival hemorrhage<br>Hematologic & oncologic: Iatrogenic bleeding<br>Nervous system: Fatigue, headache, paresthesia<br>Respiratory: Epistaxis<br>Miscellaneous: Fever |
| **Drug Interactions** | No Category X interactions noted |
| **Special Population** | N/A |
| **Pregnancy** | Adverse events were not observed in animal reproduction studies.<br>There is a risk of bleeding with caplacizumab; monitor both the mother and the newborn if exposure occurs during pregnancy. |

| | |
|---|---|
| | Acquired thrombotic thrombocytopenic purpura, when first diagnosed during pregnancy, is also associated with adverse pregnancy outcomes.<br>Treatment generally follows current recommendations which include plasma exchange, plasma infusion, and/or immunosuppressive therapy.<br>Pregnant females were excluded from the initial caplacizumab studies. |
| **Lactation** | It is not known if caplacizumab is present in breast milk.<br>According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. |
| **Contraindications** | Previous severe hypersensitivity (eg, urticaria) to caplacizumab or any component of the formulation. |
| **Monitoring Requirements** | Consider monitoring ADAMTS13 activity levels. Monitor for signs/symptoms of bleeding, especially in patients at increased risk (severe hepatic impairment or who are on concurrent medications affecting hemostasis and coagulation). |
| **Precautions** | **Bleeding**: The risk of bleeding is increased in patients with underlying coagulopathies (eg, hemophilia, or other coagulation factor deficiencies) and with concomitant use of caplacizumab with medications affecting hemostasis and coagulation; avoid concomitant use with antiplatelets or anticoagulants.<br>Withhold caplacizumab for 7 days prior to elective surgery, dental procedures, or other invasive interventions. If emergency surgery is needed, the use |

| | |
|---|---|
| | of von Willebrand factor concentrate may be considered to correct hemostasis. After the risk of surgical bleeding has resolved, and caplacizumab has been resumed, monitor closely for signs of bleeding.<br>**Hypersensitivity**: Urticaria has been reported<br>**Hepatic impairment**: Use with caution in patients with severe acute or chronic hepatic impairment (due to the potential increased risk of bleeding); monitor closely. |
| **Black Box Warning** | N/A |
| **REMS** | N/A |

## HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Thrombotic Thrombocytopenic Purpura treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Caplacizumab.**

**Table 7.** Caplacizumab HTA Analysis

| MEDICATION | AGENCY | DATE – HTA RECOMMENDATION |
|---|---|---|
| **Caplacizumab** | NICE[15] | **December 16, 2020**<br>Caplacizumab with plasma exchange and immunosuppression is **recommended**, within its marketing authorization, as an option for treating an acute episode of acquired thrombotic thrombocytopenic purpura (TTP) in adults, and in young people aged 12 years and over who weigh at least 40 kg. Treatment should be started and supervised by physicians experienced in managing thrombotic microangiopathies. |
| | CADTH[16] | **April 5, 2023**<br>**Do not reimburse.** |

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| | | Evidence from clinical trials were unable to demonstrate that Caplacizumab improved survival and quality of life, minimized organ damage, or prevented long-term aTTP recurrence. Although results showed that Caplacizumab reduced time to platelet normalization compared with placebo in patients with aTTP who received PE and immunosuppressive therapy, CADTH Canadian Drug Expert Committee was unable to determine how this correlated with the previously mentioned clinical outcomes.<br>Evidence from an integrated analysis of clinical trials and several sources of real-world evidence were unable to clearly demonstrate whether Caplacizumab provides benefits when added to PE and immunosuppressive therapy due to limitations associated with the methodology.<br>Based on the evidence reviewed, it remains uncertain whether Caplacizumab meets the needs identified by patients of improving survival and quality of life, preventing disease complications, reducing the need for PE, and preventing disease recurrence. |
| | HAS[17] | **November 02, 2021**<br>**Favorable opinion** for reimbursement in the treatment of adults experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression. |
| | IQWIG[18] | **January 2, 2019**<br>The institution reviewed caplacizumab for adults suffering from an acute aTTP episode. No English summary was available; however, it was determined that the benefit of caplacizumab, as an orphan drug, was considered as proven by its authorization and is therefore **reimbursed**. |
| | PBAC[19] | **July 2020**<br>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 |

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| | | 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 favored caplacizumab. |

**CONCLUSION STATEMENT- Caplacizumab**

Caplacizumab is recommended in addition to TPE and immunosuppression in confirmed aTTP episodes. It has a specific dosage regimen for patients aged 12 years and over who weigh at least 40 kg. An initial IV bolus of 10mg should be given at least 15 minutes before plasma exchange. A further 10mg SC should be given after the end of the plasma exchange session. A 10mg SC should be continued once daily, given after plasma exchange for the duration of plasma exchange and at least 30 days afterward. The drug has a positive recommendation from HTA bodies including NICE, IQWIG and HAS for its use in aTTP. However, PBAC and CADTH have issued negative recommendations concerning the use of Caplacizumab in this disease.

Limitations for the use of Caplacizumab include bleeding, hypersensitivity, and hepatic impairment.

### 2.1.2 Anti-CD20: Rituximab

Information on Rituximab is detailed in the table below[14]:

**Table 8.** Rituximab Drug Information

| **SCIENTIFIC NAME RITUXIMAB** | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA** | N/A |
| **US FDA** | No |
| **EMA** | No |
| **MHRA** | No |
| **PMDA** | No |
| **Indication (ICD-10)** | M31.1 |

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| **Drug Class** | Antineoplastic Agent; Antineoplastic Agent, Monoclonal Antibody; Antirheumatic, Immunosuppressant |
| **Drug Sub-class** | Anti-CD20 Monoclonal Antibody |
| **ATC Code** | L01XC02 |
| **Pharmacological Class (ASHP)** | Antineoplastic Agent |
| **DRUG INFORMATION** | |
| **Dosage Form** | Concentrate and diluent for solution for IV infusion |
| **Route of Administration** | IV Use, SQ Use |
| **Dose (Adult) [DDD]*** | *Acute treatment for initial therapy or for refractory or relapsing disease:* IV: 375 mg/m2 once weekly for 4 doses, typically in combination with a systemic glucocorticoid and plasma exchange; administer immediately following plasma exchange and allow ≥24 hours after rituximab before the next plasma exchange.<br>*Prophylactic therapy during remission (following treatment and recovery from an acute episode) with persistently low ADAMTS13 activity (eg, <20%) but normal platelet count*: Note: The decision to treat prophylactically should be based on shared decision making to consider patient preferences regarding remission versus potential rituximab toxicity.<br>IV: 375 mg/m2 once weekly for 1 to 4 doses depending on follow-up measurements of ADAMTS13 activity. Some experts may administer a single dose of 375 mg/m2 approximately once every 3 months to maintain remission in patients with multiple relapses and severe ADAMTS13 deficiency.<br>In patients undergoing plasma exchange, rituximab should be |

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| | administered after the end of the plasma exchange session.<br>PEX should be withheld for at least 4 hours after completion of rituximab.<br>Premedication with antihistaminic drugs and acetaminophen should be administered, due to the side effects of the drug. An infusion pump should be employed to increase the infusion rate gradually. |
| **Maximum Daily Dose Adults*** | N/A |
| **Dose (pediatrics)** | Immune thrombocytopenic purpura, chronic: Limited data available: Children and Adolescents: IV infusion: 375 mg/m2 once weekly for 4 doses.<br>Pretreatment with acetaminophen and an antihistamine (diphenhydramine typically used in pediatric trials) is recommended |
| **Maximum Daily Dose Pediatrics*** | N/A |
| **Adjustment** | No dosage adjustments in hepatic impairment.<br>Kidney impairment prior to treatment initiation; no adjustment necessary. Not significantly dialyzed. |
| **Prescribing edits*** | PA, ST, AGE, MD, CU |
| **AGE (Age Edit):** | Not given to children less than 6 years of age. |
| **CU (Concurrent Use Edit):** | Can be given with plasma exchange and corticosteroids |
| **G (Gender Edit):** | N/A |
| **MD (Physician Specialty Edit):** | Rituximab must be prescribed by a consultant hematologist for TTP. |
| **PA (Prior Authorization):** | Rituximab is considered as a second line therapy during the acute phase of iTTP. It is also indicated for refractory or recurrent TTP. It can also be used as prophylaxis during remission period. This drug is given as 375 mg/m2 IV once weekly for 4 doses, typically in |

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| | combination with a systemic glucocorticoid and plasma exchange. Rituximab must be prescribed by a consultant hematologist for TTP. |
| **QL (Quantity Limit):** | N/A |
| **ST (Step Therapy):** | Rituximab is considered as a second line therapy during the acute phase of iTTP. It is also indicated for refractory or recurrent TTP and as prophylaxis during remission period. |
| **EU (Emergency Use Only):** | N/A |
| **PE (Protocol Edit):** | N/A |
| **SAFETY** | |
| **Main Adverse Drug Reactions (most common and most serious)** | **Most common**: cardiac disorders, hypophosphatemia, nausea, anemia, hepatobiliary disease, antibody development, chills, fatigue, pulmonary toxicity, fever, infusion related reactions<br>**Most serious**:<br>• Hepatitis B virus reactivation<br>• Hypogammaglobulinemia and Infection<br>• Infusion-related reactions<br>• Progressive multifocal leukoencephalopathy (PML) |
| **Drug Interactions*** | **Category X:**<br>• Abatacept<br>• Abrocitinib<br>• Adalimumab<br>• Adenovirus (Types 4, 7) Vaccine<br>• Anakinra<br>• Anifrolumab<br>• Baricitinib<br>• BCG (Intravesical)<br>• BCG Vaccine (Immunization)<br>• Belimumab<br>• Brivudine [INT]<br>• Certolizumab Pegol<br>• Cholera Vaccine |

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| | • Cladribine<br>• Dengue Tetravalent Vaccine (Live)<br>• Deucravacitinib<br>• Dipyrone<br>• Ebola Zaire Vaccine (Live)<br>• Etanercept<br>• Fexinidazole<br>• Filgotinib<br>• Golimumab<br>• InFLIXimab<br>• Influenza Virus Vaccine (Live/Attenuated)<br>• Japanese Encephalitis Virus Vaccine (Live/Attenuated)<br>• Measles, Mumps, and Rubella Virus Vaccine<br>• Measles, Mumps, Rubella, and Varicella Virus Vaccine<br>• Mumps Virus Vaccine<br>• Nadofaragene Firadenovec<br>• Natalizumab<br>• Pimecrolimus<br>• Poliovirus Vaccine (Live/Bivalent/Oral)<br>• Poliovirus Vaccine (Live/Trivalent/Oral)<br>• Rotavirus Vaccine<br>• Ruxolitinib (Topical)<br>• Sarilumab<br>• Smallpox Vaccine Live<br>• Tacrolimus (Topical)<br>• Talimogene Laherparepvec<br>• Tertomotide<br>• Tocilizumab<br>• Tofacitinib<br>• Typhoid Vaccine<br>• Upadacitinib<br>• Varicella Virus Vaccine<br>• Yellow Fever Vaccine |

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| | • Zoster Vaccine (Live/Attenuated) |
| **Special Population** | **Pediatric**: Prior to rituximab therapy, patients should be brought up to date with all nonlive vaccination if possible; any nonlive vaccines should be administered ≥4 weeks prior to first rituximab dose. Pretreatment with acetaminophen and an antihistamine (diphenhydramine typically used in pediatric trials) is recommended for all indications.<br>**Older adult**: There is a higher risk of cardiac (supraventricular arrhythmia) and pulmonary adverse events (pneumonia, pneumonitis), and the incidence of grade 3 or 4 adverse reactions are higher in patients ≥65 years of age. |
| **Pregnancy** | Rituximab crosses the placenta and can be detected in the newborn. Although approved for the treatment of rheumatoid arthritis, based on available data, rituximab should be discontinued once pregnancy is detected in patients treated for rheumatic and musculoskeletal diseases; treatment during pregnancy should only be considered for pregnant patients with life- or organ-threatening disease. |
| **Lactation** | Rituximab is present in breast milk. According to the manufacturer, breastfeeding is not recommended during treatment and for 6 months after the last dose of rituximab. However, based on available data, rituximab is considered compatible with breastfeeding in patients treated for rheumatic and musculoskeletal diseases. In addition, rituximab is unlikely to be absorbed by the infant |

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| | gastrointestinal tract following exposure via breast milk. |
| **Contraindications** | There are no contraindications listed in the manufacturer's US labeling.<br>Canadian labeling: Known type 1 hypersensitivity or anaphylactic reaction to murine proteins, Chinese Hamster Ovary (CHO) cell proteins, or any component of the formulation; patients who have or have had progressive multifocal leukoencephalopathy (PML); patients with severe, active infections |
| **Monitoring Requirements** | Obtain CBC with differential (weekly to monthly intervals), peripheral CD20* cells, HAMA/HACA titers, and renal function tests. Screen for HBV infection prior to initiation. Monitor vital signs, fluid balance and for infusion reaction. Obtain cardiac monitoring during and after infusion in rheumatoid arthritis patients and in patients with pre-existing cardiac disease. Assess for signs of progressive multifocal leukoencephalopathy and mucocutaneous reactions. |
| **Precautions** | • **Bowel obstruction/perforation**: Abdominal pain, bowel obstruction, and perforation have been reported<br>• **Cytopenias**: Rituximab is associated with lymphopenia, leukopenia, neutropenia, thrombocytopenia, and anemia; the duration of cytopenias may be prolonged and may extend months beyond treatment.<br>• **Renal toxicity**: May cause fatal renal toxicity in patients with non-Hodgkin lymphomas (NHL).<br>• **Tumor lysis syndrome** leading to acute renal failure requiring dialysis (sometimes fatal) may occur within 12 to 24 hours following the first dose |

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| | when used as a single agent in the treatment of NHL.<br>• **Granulomatosis with polyangiitis/microscopic polyangiitis**: The safety of concomitant immunosuppressants other than corticosteroids has not been evaluated in patients with granulomatosis with polyangiitis or microscopic polyangiitis after rituximab-induced B-cell depletion.<br>• **Pemphigus vulgaris**: The safety of concomitant immunosuppressants other than corticosteroids has not been evaluated in patients with pemphigus vulgaris after rituximab-induced B-cell depletion.<br>• Some dosage forms may contain polysorbate 80 (also known as Tweens). Hypersensitivity reactions, usually a delayed reaction, have been reported.<br>• **Immunizations**: In the oncology setting, live vaccines should not be given before or during rituximab treatment |
| **Black Box Warning** | • Infusion-related reactions<br>• Mucocutaneous reactions<br>• Hepatitis B virus reactivation: some cases resulting in fulminant hepatitis, hepatic failure, and death.<br>• Progressive multifocal leukoencephalopathy |
| **REMS** | N/A |

## HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Thrombotic Thrombocytopenic Purpura treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute

Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Rituximab.**

**Table 9.** Rituximab HTA Analysis

| MEDICATION | AGENCY | DATE – HTA RECOMMENDATION |
|---|---|---|
| **Rituximab** | NICE | N/A |
| | CADTH | N/A |
| | HAS | N/A |
| | IQWIG | N/A |
| | PBAC | N/A |

**CONCLUSION STATEMENT- Rituximab**

Rituximab is considered as a second line therapy during the acute phase of iTTP. It is also indicated for refractory or recurrent TTP. It can also be used as prophylaxis during remission period. This drug is given as 375 mg/m2 IV once weekly for 4 doses, typically in combination with a systemic glucocorticoid and plasma exchange. Rituximab must be prescribed by a consultant hematologist for TTP. There are no HTA recommendations for its use in TTP. Limitations for the use of Rituximab include infusion related reactions, hepatitis B virus reactivation, and Progressive Multifocal Leukoencephalopathy.

## 2.2 Immunosuppressive Agents

### 2.2.1 Mycophenolate Mofetil

Information on Mycophenolate Mofetil is detailed in the table below [14]:

**Table 10.** Mycophenolate Mofetil Drug Information

| SCIENTIFIC NAME MYCOPHENOLATE MOFETIL | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA Approval** | No |
| **US FDA** | No |
| **EMA** | No |
| **MHRA** | No |
| **PMDA** | No |
| **Indication (ICD-10)** | M31.1 |

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| **Drug Class** | IMMUNOSUPPRESSANTS |
| **Drug Sub-class** | SELECTIVE IMMUNOSUPPRESSANTS |
| **ATC Code** | L04AA06 |
| **Pharmacological Class (ASHP)** | Immunosuppressant agent |
| **DRUG INFORMATION** | |
| **Dosage Form** | Film-coated tablet, capsule |
| **Route of Administration** | Oral use |
| **Dose (Adult) [DDD]*** | As per the "Mycophenolate Mofetil for First-Line Treatment of Immune Thrombocytopenia" study published in NEJM on September 2021, the drug regimen was the following: Starting dose of 500 mg twice daily (along with a glucocorticoid) for 2 weeks, at which time the dose was increased to 750 mg twice daily if the patient had no side effects; after 2 more weeks (4 weeks after initiation of treatment with mycophenolate mofetil), the dose was increased to 1 g twice daily if the patient had no side effects. The mycophenolate mofetil dosing algorithm was followed regardless of the patient's platelet count. After 6 months of mycophenolate mofetil therapy, the dose for all patients who had a complete response to mycophenolate mofetil (platelet count >100×109 per liter) was reduced by 250 mg each month, with the goal of continuing the lowest dose that achieved a hemostatic (safe) platelet count (>30×109 per liter) and ensuring that patients whose disease had gone into spontaneous remission did not continue to take the drug indefinitely |
| **Maximum Daily Dose Adults*** | Cellcept: 2g daily dose |
| **Dose (pediatrics)** | N/A |
| **Maximum Daily Dose Pediatrics*** | N/A |

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| **Adjustment** | Neutropenia (ANC <1.3 x 103/mcL): Dosing should be interrupted, or the dose reduced. No hepatic dose adjustment. Consider therapeutic drug monitoring for eGFR<60 mL/ min/ 1.73 m2 when available. Use with caution for eGFR <25 mL/ min/ 1.73 m2 consider limiting dose to 1 g twice daily or delayed release 720 mg twice daily. Not dialyzable in intermittent hemodialysis or peritoneal dialysis. Removal by CRRT or PIRRT is expected to be insignificant for eGFR<25 <25 mL/ min/ 1.73 m2[20]. No hepatic or renal adjustment for pediatric doses. Not removed by dialysis. |
| **Prescribing edits*** | CU, AGE, MD, ST |
| **AGE (Age Edit)** | Not to be given to patients less than 3 months old. |
| **CU (Concurrent Use Edit)** | Can be used in patients who are taking plasma exchange and corticosteroids. |
| **G (Gender Edit**) | N/A |
| **MD (Physician Specialty Edit)** | Only physicians experienced in hematology should prescribe Mycophenolate Mofetil. |
| **PA (Prior Authorization)** | N/A |
| **QL (Quantity Limit)** | N/A |
| **ST (Step Therapy)** | Can be used in combination as first line therapy with corticosteroids in parallel to plasma exchange. Some small sized studies have examined its use in relapsed TTP who received multiple lines of treatment, however, a formal longer is warranted. |
| **EU (Emergency Use Only)** | N/A |
| **PE (Protocol Edit)** | N/A |
| **SAFETY** | |
| **Main Adverse Drug Reactions (most common and most serious)** | **Most common:** edema, hypertension, hypotension, hypercholesterolemia, hyperglycemia, hypokalemia and |

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| | hypomagnesemia, abdominal pain, nausea, vomiting, anemia, leukopenia<br>**<u>Most serious</u>**: Acute inflammatory syndrome, Bone marrow suppression, GI effects, Infection, Lymphoproliferative disorders, Pure red cell aplasia |
| **Drug Interactions*** | **<u>Category X</u>**:<br>• Abrocitinib<br>• Adenovirus (Types 4, 7) Vaccine<br>• Baricitinib<br>• BCG (Intravesical)<br>• BCG Vaccine (Immunization)<br>• Brivudine [INT]<br>• Cholera vaccine<br>• Cholestyramine Resin<br>• Cladribine<br>• Colesevelam<br>• Colestipol<br>• Dengue Tetravalent Vaccine (Live)<br>• Deucravacitinib<br>• Ebola Zaire Vaccine (Live)<br>• Filgotinib<br>• Influenza Virus Vaccine (Live/Attenuated)<br>• Japanese Encephalitis Virus Vaccine (Live/Attenuated)<br>• Measles, Mumps, and Rubella Virus Vaccine<br>• Measles, Mumps, Rubella, and Varicella Virus Vaccine<br>• Mumps Virus Vaccine<br>• Nadofaragene Firadenovec<br>• Natalizumab<br>• Pimecrolimus<br>• Poliovirus Vaccine (Live/Bivalent/Oral)<br>• Poliovirus Vaccine (Live/Trivalent/Oral)<br>• Rotavirus Vaccine<br>• Ruxolitinib (Topical)<br>• Smallpox Vaccine Live |

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| | • Tacrolimus (Topical)<br>• Talimogene Laherparepvec<br>• Tertomotide<br>• Tofacitinib<br>• Typhoid Vaccine<br>• Upadacitinib<br>• Varicella Virus Vaccine<br>• Yellow Fever Vaccine<br>Zoster Vaccine (Live/Attenuated) |
| **Special Population** | **Older Adult**<br>Dosage is the same as for younger patients; however, dosing should be cautious due to possibility of increased hepatic, renal, or cardiac dysfunction. Patients ≥65 years of age may be at an increased risk of certain infections, GI hemorrhage, and pulmonary edema, as compared to patients <65 years of age. |
| **Pregnancy** | [US Boxed Warning]: Use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Avoid if safer treatment options are available. |
| **Lactation** | It is not known if mycophenolate is present in breast milk.<br>According to the manufacturer, the decision to breastfeed during therapy should consider the risks and benefits. |
| **Contraindications** | Hypersensitivity to any component of the formulation. IV formulation is also contraindicated in patients who are allergic to polysorbate 80 (Tween). Additional contraindications (not in the US labeling): Pregnancy; women of childbearing potential and not using highly effective contraceptive methods; or not providing a pregnancy test result; breastfeeding. |
| **Monitoring Requirements** | Obtain CBC, renal function tests, and liver function tests. Assess other |

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| | medications patient is taking. Patients with diabetes should monitor glucose levels closely. Assess for signs and symptoms of infection, neurological symptoms, skin lesions suspicious of skin cancer, lymphoma, pure red cell aplasia, and autoimmune hemolytic anemia. Monitor neurological symptoms, and signs of pure red cell aplasia or autoimmune hemolytic anemia. |
| **Precautions** | May cause CNS depression. Use caution in patients with serious digestive system disease. Avoid in patients with hypoxanthine-guanine phosphoribosyl transferase deficiency. Not interchangeable with mycophenolate sodium without healthcare supervision: different rates of absorption. Some dosage forms may contain phenylalanine. Some dosage forms may contain polysorbate 80 also known as Tweens. Patients should not donate blood or blood products during treatment and for at least 6 weeks after the last dose. Abrupt cessation in patients with myasthenia gravis may result in deterioration of symptoms and possible myasthenic crisis. Avoid live attenuated vaccines. Never administer IV solution by rapid or bolus injection. |
| **Black Box Warning** | • Should only be prescribed by an experienced physician in immunosuppressive therapy.<br>• Serious Infections<br>• Malignancies: lymphoma and other malignancies, particularly of the skin<br>• Embryo-fetal toxicity. Avoid if safer options available |
| **REMS** | REMS Drugs COVID-19 Safety Alert: to assure safe use: consider whether there |

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| | are compelling reasons or not to complete these requirements during this public health emergency and weigh with the patient the benefits and risks of continuing treatment in the absence of the laboratory testing and imaging studies. |

## HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Thrombotic Thrombocytopenic Purpura treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Mycophenolate Mofetil.**

**Table 11.** Mycophenolate Mofetil HTA Analysis

| MEDICATION | AGENCY | DATE – HTA RECOMMENDATION |
|---|---|---|
| **Mycophenolate Mofetil** | NICE | N/A |
| | CADTH | N/A |
| | HAS | N/A |
| | IQWIG | N/A |
| | PBAC | N/A |

### CONCLUSION STATEMENT- Mycophenolate Mofetil

The drug can be used in combination as first line therapy with corticosteroids in parallel to plasma exchange. Some small sized studies have examined its use in relapsed TTP who received multiple lines of treatment, however, a formal longer is warranted. Only physicians experienced in hematology should prescribe Mycophenolate Mofetil. In case a patient develops gastrointestinal adverse effects, Mycophenolate Sodium (180mg or 360mg) can be used as an alternative. There are no HTA recommendations regarding the use of Mycophenolate Mofetil in TTP. Limitations for the use of Mycophenolate Mofetil include serious infections and malignancies.

### 2.2.2 Cyclosporine

Information on Cyclosporine is detailed in the table below[14]:

**Table 12.** Cyclosporine Drug Information

| **SCIENTIFIC NAME CYCLOSPORINE** | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA** | N/A |
| **US FDA** | No |
| **EMA** | No |
| **MHRA** | No |
| **PMDA** | Off label |
| **Indication (ICD-10)** | M31.1 |
| **Drug Class** | Immunosuppressant Agent |
| **Drug Sub-class** | Calcineurin Inhibitor |
| **ATC Code** | L04AD01 |
| **Pharmacological Class (ASHP)** | Immunosuppressant Agent |
| **DRUG INFORMATION** | |
| **Dosage Form** | Capsule, hard |
| **Route of Administration** | Oral Use |
| **Dose (Adult) [DDD]** | Oral cyclosporine 4 mg/kg/day is administered in two divided doses.<br>Blood levels of cyclosporine should be monitored to maintain a trough level of approximately 100–200 ng/mL. |
| **Maximum Daily Dose Adults** | N/A |
| **Dose (pediatrics)** | N/A |
| **Maximum Daily Dose Pediatrics** | N/A |
| **Adjustment** | Severe hepatic impairment: There are no dosage adjustments provided in the manufacturer's labeling; however, metabolism is extensively hepatic (exposure is increased). Monitor blood concentrations; may require dose reduction.<br>Kidney impairment prior to treatment initiation: no adjustment necessary. |

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| | During treatment: Nontransplant indications: If serum creatinine increases 25% to 30% above baseline (measured on 2 separate occasions at least 2 weeks apart), or by ≥50% at any time during therapy, reduce dose by 25% to 50% and monitor serum creatinine every 2 weeks for 1 month. If serum creatinine does not decrease to within 25% to 30% of baseline, reduce dose by 25% to 50% and monitor serum creatinine every 2 weeks for 1 month. If serum creatinine does not decrease to within 25% to 30% of baseline, discontinue cyclosporine.<br>For patients receiving renal replacement: Consider temporary interruption of therapy or switching to an alternative agent to help promote renal recovery and preserve residual kidney function if other factors contributing to decreased kidney function cannot be mitigated. Continued use should only be considered if benefits outweigh risks of further kidney injury |
| **Prescribing edits** | ST, MD |
| **AGE (Age Edit):** | N/A |
| **CU (Concurrent Use Edit):** | N/A |
| **G (Gender Edit):** | N/A |
| **MD (Physician Specialty Edit):** | Only physicians experienced in immunosuppressive therapy and hematology should prescribe Cyclosporine. |
| **PA (Prior Authorization):** | N/A |
| **QL (Quantity Limit):** | N/A |
| **ST (Step Therapy):** | This drug is recommended as an alternative option for recurrent or refractory TTP |
| **EU (Emergency Use Only):** | N/A |

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| **PE (Protocol Edit):** | N/A |
| **SAFETY** | |
| **Main Adverse Drug Reactions (most common and most serious)** | **Most common:**<br>Hypertension, Hirsutism, Urinary tract infection, Tremor<br>**Most serious:**<br>• Diabetes mellitus<br>• Drug-induced gingival overgrowth<br>• Drug-induced thrombotic microangiopathy<br>• Hepatotoxicity<br>• Hyperkalemia<br>• Hypertension<br>• Infections<br>• Malignancy<br>• Nephrotoxicity<br>• Neurotoxicity |
| **Drug Interactions*** | **Category X:**<br>• Abrocitinib<br>• Adenovirus (Types 4, 7) Vaccine<br>• Aliskiren<br>• AMILoride<br>• Asunaprevir<br>• Atorvastatin<br>• Baricitinib<br>• BCG (Intravesical)<br>• BCG Vaccine (Immunization)<br>• Bilastine Depends on Renal Function<br>• Bosentan<br>• Brivudine [INT]<br>• Cholera Vaccine<br>• Cladribine<br>• Dengue Tetravalent Vaccine (Live)<br>• Deucravacitinib<br>• Disulfiram Depends on Dosage Form<br>• DOXOrubicin Conventional<br>• Dronedarone<br>• Ebola Zaire Vaccine (Live) |

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| | • Elagolix<br>• Elagolix, Estradiol, and Norethindrone<br>• Elbasvir and Grazoprevir<br>• Eplerenone<br>• Erdafitinib<br>• Fexinidazole<br>• Filgotinib<br>• Foscarnet<br>• Fusidic Acid (Systemic)<br>• Grapefruit Juice Depends on Route<br>• Influenza Virus Vaccine (Live/Attenuated)<br>• Japanese Encephalitis Virus Vaccine (Live/Attenuated)<br>• Lasmiditan<br>• Lercanidipine<br>• Lovastatin<br>• Measles, Mumps, and Rubella Virus Vaccine<br>• Measles, Mumps, Rubella, and Varicella Virus Vaccine<br>• Methotrimeprazine Depends on Dosage Form<br>• Mifamurtide<br>• MiFEPRIStone Depends on Indication<br>• Mumps Virus Vaccine<br>• Nadofaragene Firadenovec<br>• Natalizumab<br>• Ornidazole Depends on Dosage Form and International labeling<br>• Pacritinib<br>• PAZOPanib<br>• Pimecrolimus<br>• Pimozide<br>• Pitavastatin<br>• Poliovirus Vaccine (Live/Bivalent/Oral)<br>• Poliovirus Vaccine (Live/Trivalent/Oral)<br>• Red Yeast Rice |

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| | • Revefenacin<br>• Rotavirus Vaccine<br>• Ruxolitinib (Topical)<br>• Secnidazole Depends on Dosage Form<br>• Simeprevir<br>• Simvastatin<br>• Sirolimus (Protein Bound)<br>• Smallpox Vaccine Live<br>• Sparsentan<br>• XSpironolactone<br>• Tacrolimus (Systemic)<br>• Tacrolimus (Topical)<br>• Talimogene Laherparepvec<br>• Taurursodiol<br>• Tertomotide<br>• Tofacitinib<br>• Topotecan Depends on Route<br>• Treosulfan<br>• Triamterene<br>• Typhoid Vaccine<br>• Upadacitinib<br>• Varicella Virus Vaccine<br>• VinCRIStine (Liposomal)<br>• Voxilaprevir<br>• Yellow Fever Vaccine<br>• Zavegepant<br>• Zoster Vaccine (Live/Attenuated) |
| **Special Population** | Older Adult Considerations<br>Cyclosporine may be used in combination therapy for the treatment of severe rheumatoid arthritis. Monitor renal function closely during therapy and decrease dose as needed. |
| **Pregnancy** | Cyclosporine crosses the placenta. Cyclosporine can be used during pregnancy for refractory cases of lupus nephritis and other rheumatic and musculoskeletal diseases in patients |

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| | who are not able to use alternative therapies; however, close monitoring of blood pressure is recommended. |
| **Lactation** | Cyclosporine is present in breast milk. Due to the potential for serious adverse in the breastfeeding infant, the manufacturer recommends a decision be made to discontinue cyclosporine or to discontinue breastfeeding, considering the importance of treatment to the mother. |
| **Contraindications** | Hypersensitivity to cyclosporine or any component of the formulation. IV cyclosporine is contraindicated in hypersensitivity to polyoxyethylated castor oil.<br>Additional contraindications (not in the US labeling): Concurrent use with bosentan; rheumatoid arthritis and psoriasis patients with primary or secondary immunodeficiency excluding autoimmune disease, uncontrolled infection, or malignancy (excluding non-melanoma skin cancer). |
| **Monitoring Requirements** | Obtain plasma concentrations, renal function tests, liver function tests, and serum glucose. Monitor blood pressure periodically and with addition, modification, or deletion of other medications. Assessing for hypersensitivity reactions with IV use. Assess for signs and symptoms of liver toxicity, secondary malignancy, diabetes, and infection. Assess for progressive cognitive or motor deficits. Consider MRI if posterior reversible encephalopathy syndrome is suspected. Assess other medications patient is taking; alternative therapy or dosage adjustment may be needed. When transferring patients with previously |

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| | poor absorption of cyclosporine (non-modified), monitor trough levels at least twice weekly. For myasthenia gravis patients, abrupt cessation of cyclosporine may cause rapid deterioration of myasthenic symptoms and myasthenic crisis. |
| **Precautions** | Product may contain corn oil or ethanol or polyoxyethylated castor oil or propylene glycol. Discontinuation of therapy: Myasthenia gravis: Abrupt cessation of this or any immunosuppressant, especially in clinically unstable individuals, may result in rapid deterioration of myasthenic symptoms and possibly myasthenic crisis.<br>Vaccines: Live, attenuated vaccines may be less effective; vaccination should be avoided. |
| **Black Box Warning** | • Only health care providers experienced in the management of systemic immunosuppressive therapy for the indicated disease should prescribe cyclosporine.<br>• Immunosuppression<br>• Erratic absorption and bioavailability<br>• Psoriasis patients previously treated with psoralens plus ultraviolet A (PUVA) and, to a lesser extent, methotrexate or other immunosuppressive agents, ultraviolet B (UVB), coal tar, or radiation therapy, are at an increased risk of developing skin malignancies when taking cyclosporine.<br>• Hypertension/nephrotoxicity |
| **REMS** | N/A |

**HEALTH TECHNOLOGY ASSESSMENT (HTA)**

The table below lists the HTA reviews and recommendations of Thrombotic Thrombocytopenic Purpura (TTP) treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Cyclosporine.**

**Table 13.** Cyclosporine HTA Analysis

| MEDICATION | AGENCY | DATE – HTA RECOMMENDATION |
|---|---|---|
| **Cyclosporine** | NICE | N/A |
| | CADTH | N/A |
| | HAS | N/A |
| | IQWIG | N/A |
| | PBAC | N/A |

**CONCLUSION STATEMENT- Cyclosporine**

This drug is recommended as an alternative option for recurrent or refractory TTP. This drug is given as oral cyclosporine 4 mg/kg/day is administered in two divided doses.
Blood levels of cyclosporine should be monitored to maintain a trough level of approximately 100–200 ng/mL. Only physicians experienced in immunosuppressive therapy and hematology should prescribe Cyclosporine. There are no HTA recommendations regarding the use of Cyclosporine in TTP. Limitations for the use of Cyclosporine include nephrotoxicity, hypertension, and psoriasis.

### 2.2.3 Dexamethasone

Information on Dexamethasone are detailed in the table below[14]:

**Table 14.** Dexamethasone Drug Information

| SCIENTIFIC NAME DEXAMETHASONE | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA Approval** | Yes |
| **US FDA** | Yes |
| **EMA** | Yes |

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| **MHRA** | Yes |
| **PMDA** | Yes |
| **Indication (ICD-10)** | M31.1 |
| **Drug Class** | Anti-inflammatory Agent |
| **Drug Sub-class** | Corticosteroids |
| **ATC Code** | H02AB02 |
| **Pharmacological Class (ASHP)** | Systemic Corticosteroids |
| **DRUG INFORMATION** | |
| **Dosage Form** | Oral solution, solution for injection |
| **Route of Administration** | Oral and intravenous use |
| **Dose (Adult) [DDD]** | Oral, IV: 40 mg once daily for 4 days and then stop (no taper); may be repeated up to 3 times if inadequate response. |
| **Maximum Daily Dose Adults** | N/A |
| **Dose (pediatrics)** | N/A |
| **Maximum Daily Dose Pediatrics** | N/A |
| **Adjustment** | There are no dosage adjustments provided in the manufacturer's labeling. |
| **Prescribing edits*** | MD, QL, ST, CU |
| **AGE (Age Edit)** | N/A |
| **CU (Concurrent Use Edit)** | Can be used with plasma exchange, immunosuppressive therapies, or other drugs to treat TTP and its complications |
| **G (Gender Edit)** | N/A |
| **MD (Physician Specialty Edit)** | Dexamethasone is to be prescribed by a physician who is experienced in the treatment of TTP (consultant hematologist) |
| **PA (Prior Authorization)** | N/A |
| **QL (Quantity Limit)** | The duration of treatment is a few days. A longer duration of steroids may be needed, and this can usually be given orally but this will be decided following discussion with the consultant hematologist. |
| **ST (Step Therapy)** | Corticosteroids are recommended first line treatment for TTP |
| **EU (Emergency Use Only)** | N/A |

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| **PE (Protocol Edit)** | N/A |
| **SAFETY** | |
| **Main Adverse Drug Reactions (most common and most serious)** | **Most common:** Hypertension, tachycardia, nausea.<br>**Most serious:** Adrenal suppression (tertiary adrenal insufficiency), Cushing syndrome, hyperglycemia, apathy/depression, peptic ulcers, infections, osteoporosis, glaucoma and cataracts. |
| **Drug Interactions*** | **Category X:**<br>Aldesleukin<br>BCG (Intravesical)<br>Brivudine<br>Cladribine<br>Desmopressin<br>Disulfiram<br>Fexinidazole<br>Fusidic Acid (Systemic)<br>Indium 111 Capromab Pendetide<br>Lapatinib<br>Macimorelin<br>Methotrimeprazine<br>Mifamurtide<br>MiFEPRIStone<br>Nadofaragene Firadenovec<br>Natalizumab<br>Ornidazole<br>Pimecrolimus<br>Rilpivirine<br>Ritlecitinib<br>Ruxolitinib (Topical)<br>Secnidazole<br>Simeprevir<br>Tacrolimus (Topical)<br>Talimogene Laherparepvec<br>Tertomotide |

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| **Special Population** | **Older adults:** Use with caution in elderly patients with the smallest possible effective dose for the shortest duration.<br>**Pediatrics:** May affect growth velocity; growth should be routinely monitored in pediatric patients. |
| **Pregnancy** | Teratogenic effects: Pregnancy Category C<br>Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. |
| **Lactation** | Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Because of the potential for serious adverse reactions in nursing infants from corticosteroids, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. |
| **Contraindications** | Hypersensitivity to dexamethasone or any component of the formulation; systemic fungal infections |
| **Monitoring Requirements** | Hemoglobin, occult blood loss, blood pressure, serum potassium, blood glucose, creatine kinase (if symptoms of myopathy occur), bone mineral density; intraocular pressure with systemic use >6 weeks; consider routine eye exams with chronic use; weight and height in children; hypothalamic-pituitary-adrenal axis suppression. |
| **Precautions** | **Adrenal suppression:** May cause hypercortisolism or suppression of hypothalamic-pituitary-adrenal axis, particularly in younger children.<br>**Cardiovascular disease:** Use with caution in patients with heart failure |

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| | and/or hypertension; use has been associated with fluid retention, electrolyte disturbances, and hypertension. Monitor blood pressure. Use with caution following acute myocardial infarction; corticosteroids have been associated with myocardial rupture.<br>**GI disease:** Use with caution in patients with GI diseases (diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, ulcerative colitis, abscess, or other pyogenic infection) due to GI perforation risk. Signs of GI perforation may be masked in patients receiving corticosteroid therapy.<br>**Hepatic impairment:** Use with caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention.<br>**Hepatitis B:** Reactivation may occur.<br>**Ocular disease:** Use with caution in patients with a history of ocular herpes simplex; corneal perforation has occurred; do not use in active ocular herpes simplex.<br>**Pheochromocytoma:**<br>Pheochromocytoma crisis (may be fatal) has been reported after administration of systemic corticosteroids. Consider the risk of pheochromocytoma crisis in patients with suspected or confirmed pheochromocytoma.<br>**Renal impairment:** Use with caution in patients with renal impairment; fluid retention may occur.<br>**Seizure disorders:** Use corticosteroids with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis. |

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|---|---|
| | **Systemic sclerosis:** Use with caution in patients with systemic sclerosis; an increase in scleroderma renal crisis incidence has been observed with corticosteroid use. Monitor BP and renal function in patients with systemic sclerosis treated with corticosteroids.<br>**Thyroid disease:** Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid patients.<br>**Immunizations:** Avoid administration of live or live attenuated vaccines in patients receiving immunosuppressive doses of corticosteroids. Non-live or inactivated vaccines may be administered, although the response cannot be predicted.<br>**Propylene glycol:** Some dosage forms may contain propylene glycol; large amounts are potentially toxic and have been associated hyperosmolality, lactic acidosis, seizures, and respiratory depression; use caution.<br>**Sulfite:** Some products may contain sodium sulfite, a sulfite that may cause allergic-type reactions including anaphylaxis and life-threatening or less severe asthmatic episodes in susceptible patients. |
| **Black Box Warning** | N/A |
| **REMS** | N/A |

## HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of TTP treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health

Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Dexamethasone.**

**Table 15.** Dexamethasone HTA Analysis

| MEDICATION | AGENCY | DATE – HTA RECOMMENDATION |
|---|---|---|
| **Dexamethasone** | NICE | Not available |
| | CADTH | Not applicable |
| | HAS | Not applicable |
| | IQWIG | Not applicable |
| | PBAC | Not available |

**CONCLUSION STATEMENT- Dexamethasone**

Corticosteroids are recommended as first line agents for the management of TTP. They can be used in combination with plasma exchange, immunosuppressive therapies or other drugs used in the management of TTP and its complications. Dexamethasone is given at 40 mg once daily for 4 days and then stop (no taper); may be repeated up to 3 times if inadequate response. The duration of treatment is a few days. A longer duration of steroids may be needed, and this can usually be given orally but this will be decided following discussion with the consultant hematologist.

Dexamethasone is to be prescribed by a physician who is experienced in the treatment of TTP (consultant hematologist) Its use is limited by the heightened risk of developing adrenal suppression (tertiary adrenal insufficiency), Cushing syndrome, hyperglycemia, apathy/depression, peptic ulcers, infections, osteoporosis, glaucoma, and cataracts.

### 2.2.4 Prednisone

Information on Prednisone are detailed in the table below[14]:

**Table 16.** Prednisone Drug Information

| SCIENTIFIC NAME<br>Prednisone | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA Approval** | Yes |
| **US FDA** | Yes |
| **EMA** | Yes |
| **MHRA** | Yes |

| | |
|---|---|
| **PMDA** | Yes |
| **Indication (ICD-10)** | M31.1 |
| **Drug Class** | Anti-inflammatory Agent |
| **Drug Sub-class** | Corticosteroids |
| **ATC Code** | H02AB02 |
| **Pharmacological Class (ASHP)** | Systemic Corticosteroids |
| **DRUG INFORMATION** | |
| **Dosage Form** | Tablet |
| **Route of Administration** | Oral |
| **Dose (Adult) [DDD]** | Oral: 1 mg/kg/day (range: 0.5 to 2 mg/kg/day; maximum: 80 mg/day) for 1 to 3 weeks, followed by a gradual taper. Total duration of therapy should not exceed 6 weeks; if there is no response within 2 weeks, taper over 1 week and discontinue. |
| **Maximum Daily Dose Adults** | 80 mg/day |
| **Dose (pediatrics)** | N/A |
| **Maximum Daily Dose Pediatrics** | N/A |
| **Adjustment** | There are no dosage adjustments provided in the manufacturer's labeling. |
| **Prescribing edits** | MD, QL, ST, CU |
| **AGE (Age Edit)** | N/A |
| **CU (Concurrent Use Edit)** | Can be used with plasma exchange, immunosuppressive therapies, or other drugs to treat TTP and its complications |
| **G (Gender Edit)** | N/A |
| **MD (Physician Specialty Edit)** | Prednisone is to be prescribed by a physician who is experienced in the treatment of TTP (consultant hematologist) |
| **PA (Prior Authorization)** | N/A |
| **QL (Quantity Limit)** | The duration of treatment is decided following discussion with the consultant hematologist.<br>Maximum daily dose is 80 mg/day |
| **ST (Step Therapy)** | Corticosteroids are recommended first line treatment for TTP |

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|---|---|
| **EU (Emergency Use Only)** | N/A |
| **PE (Protocol Edit)** | N/A |
| **SAFETY** | |
| **Main Adverse Drug Reactions (most common and most serious)** | **Most common:** Hypertension, tachycardia, nausea.<br>**Most serious:** Adrenal suppression (tertiary adrenal insufficiency), Cushing syndrome, hyperglycemia, apathy/depression, peptic ulcers, infections, osteoporosis, glaucoma, and cataracts. |
| **Drug Interactions*** | **Category X:**<br>Aldesleukin<br>BCG (Intravesical)<br>Brivudine<br>Cladribine<br>Desmopressin<br>Disulfiram<br>Fexinidazole<br>Fusidic Acid (Systemic)<br>Indium 111 Capromab Pendetide<br>Lapatinib<br>Macimorelin<br>Methotrimeprazine<br>Mifamurtide<br>MiFEPRIStone<br>Nadofaragene Firadenovec<br>Natalizumab<br>Ornidazole<br>Pimecrolimus<br>Rilpivirine<br>Ritlecitinib<br>Ruxolitinib (Topical)<br>Secnidazole<br>Simeprevir<br>Tacrolimus (Topical)<br>Talimogene Laherparepvec<br>Tertomotide |

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|---|---|
| **Special Population** | **Older adults:** Use with caution in elderly patients with the smallest possible effective dose for the shortest duration.<br>**Pediatrics:** May affect growth velocity; growth should be routinely monitored in pediatric patients. |
| **Pregnancy** | Teratogenic effects: Pregnancy Category C<br>Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. |
| **Lactation** | Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Because of the potential for serious adverse reactions in nursing infants from corticosteroids, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. |
| **Contraindications** | Hypersensitivity to dexamethasone or any component of the formulation; systemic fungal infections |
| **Monitoring Requirements** | Hemoglobin, occult blood loss, blood pressure, serum potassium, blood glucose, creatine kinase (if symptoms of myopathy occur), bone mineral density; intraocular pressure with systemic use >6 weeks; consider routine eye exams with chronic use; weight and height in children; hypothalamic-pituitary-adrenal axis suppression. |
| **Precautions** | **Adrenal suppression:** May cause hypercortisolism or suppression of hypothalamic-pituitary-adrenal axis, particularly in younger children.<br>**Cardiovascular disease:** Use with caution in patients with heart failure |

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| | and/or hypertension; use has been associated with fluid retention, electrolyte disturbances, and hypertension. Monitor blood pressure. Use with caution following acute myocardial infarction; corticosteroids have been associated with myocardial rupture.<br>**GI disease:** Use with caution in patients with GI diseases (diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, ulcerative colitis, abscess, or other pyogenic infection) due to GI perforation risk. Signs of GI perforation may be masked in patients receiving corticosteroid therapy.<br>**Hepatic impairment:** Use with caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention.<br>**Hepatitis B:** Reactivation may occur.<br>**Ocular disease:** Use with caution in patients with a history of ocular herpes simplex; corneal perforation has occurred; do not use in active ocular herpes simplex.<br>**Pheochromocytoma:**<br>Pheochromocytoma crisis (may be fatal) has been reported after administration of systemic corticosteroids. Consider the risk of pheochromocytoma crisis in patients with suspected or confirmed pheochromocytoma.<br>**Renal impairment:** Use with caution in patients with renal impairment; fluid retention may occur.<br>**Seizure disorders:** Use corticosteroids with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis. |

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| | **Systemic sclerosis:** Use with caution in patients with systemic sclerosis; an increase in scleroderma renal crisis incidence has been observed with corticosteroid use. Monitor BP and renal function in patients with systemic sclerosis treated with corticosteroids.<br>**Thyroid disease:** Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid patients.<br>**Immunizations:** Avoid administration of live or live attenuated vaccines in patients receiving immunosuppressive doses of corticosteroids. Non-live or inactivated vaccines may be administered, although the response cannot be predicted.<br>**Propylene glycol:** Some dosage forms may contain propylene glycol; large amounts are potentially toxic and have been associated hyperosmolality, lactic acidosis, seizures, and respiratory depression; use caution.<br>**Sulfite:** Some products may contain sodium sulfite, a sulfite that may cause allergic-type reactions including anaphylaxis and life-threatening or less severe asthmatic episodes in susceptible patients. |
| **Black Box Warning** | N/A |
| **REMS*** | N/A |

## HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of TTP treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health

Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Prednisone.**

**Table 17.** Prednisone HTA Analysis

| MEDICATION | AGENCY | DATE – HTA RECOMMENDATION |
|---|---|---|
| **Prednisone** | NICE | Not available |
| | CADTH | Not applicable |
| | HAS | Not applicable |
| | IQWIG | Not applicable |
| | PBAC | Not available |

**CONCLUSION STATEMENT- Prednisone**

Corticosteroids are recommended as first line agents for the management of TTP. They can be used in combination with plasma exchange, immunosuppressive therapies or other drugs used in the management of TTP and its complications. Prednisone is given at 1 mg/kg/day oral (range: 0.5 to 2 mg/kg/day; maximum: 80 mg/day) for 1 to 3 weeks, followed by a gradual taper. Total duration of therapy should not exceed 6 weeks; if there is no response within 2 weeks, taper over 1 week and discontinue. The duration of treatment is to be decided following discussion with the consultant hematologist.

Prednisone is to be prescribed by a physician who is experienced in the treatment of TTP (consultant hematologist) Its use is limited by the heightened risk of developing adrenal suppression (tertiary adrenal insufficiency), Cushing syndrome, hyperglycemia, apathy/depression, peptic ulcers, infections, osteoporosis, glaucoma and cataracts.

### 2.2.5 Methylprednisolone

Information on Methylprednisolone are detailed in the table below[14]:

**Table 18.** Methylprednisolone Drug Information

| SCIENTIFIC NAME Methylprednisolone | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA Approval** | Yes |
| **US FDA** | Yes |
| **EMA** | Yes |
| **MHRA** | Yes |

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|---|---|
| **PMDA** | Yes |
| **Indication (ICD-10)** | M31.1 |
| **Drug Class** | Anti-inflammatory Agent |
| **Drug Sub-class** | Corticosteroids |
| **ATC Code** | H02AB02 |
| **Pharmacological Class (ASHP)** | Systemic Corticosteroids |
| **DRUG INFORMATION** | |
| **Dosage Form** | Oral solution, solution for injection |
| **Route of Administration** | Oral and intravenous use |
| **Dose (Adult) [DDD]** | 1000 mg per day for 3-5 days |
| **Maximum Daily Dose Adults** | N/A |
| **Dose (pediatrics)** | N/A |
| **Maximum Daily Dose Pediatrics** | N/A |
| **Adjustment** | There are no dosage adjustments provided in the manufacturer's labeling. |
| **Prescribing edits** | MD, QL, ST, CU |
| **AGE (Age Edit)** | N/A |
| **CU (Concurrent Use Edit)** | Can be used with plasma exchange, immunosuppressive therapies, or other drugs to treat TTP and its complications |
| **G (Gender Edit)** | N/A |
| **MD (Physician Specialty Edit)** | Methylprednisolone is to be prescribed by a physician who is experienced in the treatment of TTP (consultant hematologist) |
| **PA (Prior Authorization)** | N/A |
| **QL (Quantity Limit)** | The duration of treatment is few days. A longer duration of steroids may be needed, and this can usually be given orally but this will be decided following discussion with the consultant hematologist. |
| **ST (Step Therapy)** | Corticosteroids are recommended first line treatment for TTP |
| **EU (Emergency Use Only)** | N/A |
| **PE (Protocol Edit)** | N/A |
| **SAFETY** | |

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|---|---|
| **Main Adverse Drug Reactions (most common and most serious)** | **Most common:** Hypertension, tachycardia, nausea.<br>**Most serious:** Adrenal suppression (tertiary adrenal insufficiency), Cushing syndrome, hyperglycemia, apathy/depression, peptic ulcers, infections, osteoporosis, glaucoma, and cataracts. |
| **Drug Interactions*** | **Category X:**<br>Aldesleukin<br>BCG (Intravesical)<br>Brivudine<br>Cladribine<br>Desmopressin<br>Disulfiram<br>Fexinidazole<br>Fusidic Acid (Systemic)<br>Indium 111 Capromab Pendetide<br>Lapatinib<br>Macimorelin<br>Methotrimeprazine<br>Mifamurtide<br>MiFEPRIStone<br>Nadofaragene Firadenovec<br>Natalizumab<br>Ornidazole<br>Pimecrolimus<br>Rilpivirine<br>Ritlecitinib<br>Ruxolitinib (Topical)<br>Secnidazole<br>Simeprevir<br>Tacrolimus (Topical)<br>Talimogene Laherparepvec<br>Tertomotide |
| **Special Population** | **Older adults:** Use with caution in elderly patients with the smallest possible effective dose for the shortest duration. |

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| | **Pediatrics:** May affect growth velocity; growth should be routinely monitored in pediatric patients. |
| **Pregnancy** | Teratogenic effects: Pregnancy Category C<br>Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. |
| **Lactation** | Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Because of the potential for serious adverse reactions in nursing infants from corticosteroids, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. |
| **Contraindications** | Hypersensitivity to dexamethasone or any component of the formulation; systemic fungal infections |
| **Monitoring Requirements** | Hemoglobin, occult blood loss, blood pressure, serum potassium, blood glucose, creatine kinase (if symptoms of myopathy occur), bone mineral density; intraocular pressure with systemic use >6 weeks; consider routine eye exams with chronic use; weight and height in children; hypothalamic-pituitary-adrenal axis suppression. |
| **Precautions** | **Adrenal suppression:** May cause hypercortisolism or suppression of hypothalamic-pituitary-adrenal axis, particularly in younger children.<br>**Cardiovascular disease:** Use with caution in patients with heart failure and/or hypertension; use has been associated with fluid retention, electrolyte disturbances, and |

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| | hypertension. Monitor blood pressure. Use with caution following acute myocardial infarction; corticosteroids have been associated with myocardial rupture.<br>**GI disease:** Use with caution in patients with GI diseases (diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, ulcerative colitis, abscess, or other pyogenic infection) due to GI perforation risk. Signs of GI perforation may be masked in patients receiving corticosteroid therapy.<br>**Hepatic impairment:** Use with caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention.<br>**Hepatitis B:** Reactivation may occur.<br>**Ocular disease:** Use with caution in patients with a history of ocular herpes simplex; corneal perforation has occurred; do not use in active ocular herpes simplex.<br>**Pheochromocytoma:**<br>Pheochromocytoma crisis (may be fatal) has been reported after administration of systemic corticosteroids. Consider the risk of pheochromocytoma crisis in patients with suspected or confirmed pheochromocytoma.<br>**Renal impairment:** Use with caution in patients with renal impairment; fluid retention may occur.<br>**Seizure disorders:** Use corticosteroids with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis.<br>**Systemic sclerosis:** Use with caution in patients with systemic sclerosis; an increase in scleroderma renal crisis incidence has been observed with |

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|---|---|
| | corticosteroid use. Monitor BP and renal function in patients with systemic sclerosis treated with corticosteroids.<br>**Thyroid disease:** Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid patients.<br>**Immunizations:** Avoid administration of live or live attenuated vaccines in patients receiving immunosuppressive doses of corticosteroids. Non-live or inactivated vaccines may be administered, although the response cannot be predicted.<br>**Propylene glycol:** Some dosage forms may contain propylene glycol; large amounts are potentially toxic and have been associated hyperosmolality, lactic acidosis, seizures, and respiratory depression; use caution.<br>**Sulfite:** Some products may contain sodium sulfite, a sulfite that may cause allergic-type reactions including anaphylaxis and life-threatening or less severe asthmatic episodes in susceptible patients. |
| **Black Box Warning** | N/A |
| **REMS*** | N/A |

## HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of TTP treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Methylprednisolone.**

**Table 19.** Methylprednisolone HTA Analysis

| MEDICATION | AGENCY | DATE – HTA RECOMMENDATION |
|---|---|---|
| **Methylprednisolone** | NICE | Not available |
| | CADTH | Not applicable |
| | HAS | Not applicable |
| | IQWIG | Not applicable |
| | PBAC | Not available |

**CONCLUSION STATEMENT- Methylprednisolone**

Corticosteroids are recommended as first line agents for the management of TTP. They can be used in combination with plasma exchange, immunosuppressive therapies or other drugs used in the management of TTP and its complications. Methylprednisolone is given at 1000 mg per day for 3-5 days. The duration of treatment is a few days. A longer duration of steroids may be needed, and this can usually be given orally but this will be decided following discussion with the consultant hematologist.

Methylprednisolone is to be prescribed by a physician who is experienced in the treatment of TTP (consultant hematologist) Its use is limited by the heightened risk of developing adrenal suppression (tertiary adrenal insufficiency), Cushing syndrome, hyperglycemia, apathy/depression, peptic ulcers, infections, osteoporosis, glaucoma, and cataracts.

### 2.2.6 Azathioprine

Information on Azathioprine is detailed in the table below[14]:

**Table 20.** Azathioprine Drug Information

| SCIENTIFIC NAME<br>Azathioprine | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA** | Yes |
| **US FDA** | Off label |
| **EMA** | Yes |
| **MHRA** | No |
| **PMDA** | No |
| **Indication (ICD-10)** | M31.1 |
| **Drug Class** | Immunosuppressant Agent |

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| **Drug Sub-class** | N/A |
| **ATC Code** | L04AX01 |
| **Pharmacological Class (ASHP)** | Immunosuppressant Agent |
| **DRUG INFORMATION** | |
| **Dosage Form** | Tablet |
| **Route of Administration** | Oral Use |
| **Dose (Adult) [DDD]** | Oral: 1 to 2 mg/kg/day. Initial response is observed at 30 to 90 days; may take up to 6 months for peak response |
| **Maximum Daily Dose Adults** | 150 mg/day |
| **Dose (pediatrics)** | Limited data available: Children ≥2 years and Adolescents: Oral: Maintenance: 2 to 2.5 mg/kg/day, rounded to the nearest 50 mg |
| **Maximum Daily Dose Pediatrics** | N/A |
| **Adjustment** | **Oral, IV:**<br>**Altered kidney function:**<br>*CrCl ≥30 mL/minute:* Initial: No dosage adjustment necessary<br>*CrCl 10 to <30 mL/minute*: Initial: Administer 75% to 100% of the usual indication-specific dose. If the initial dose is a dose range then it is recommended to begin with the lowest end of the dose range (eg, if the usual dose is 2 to 3 mg/kg once daily then administering 75% to 100% of 2 mg/kg once daily as an initial dose is recommended)<br>*CrCl <10 mL/minute*: Initial: Administer 50% to 100% of the usual indication-specific dose. If the initial dose is a dose range then it is recommended to begin with the lowest end of the dose range (eg, if the usual dose is 2 to 3 mg/kg once daily then administering 50% to 100% of 2 mg/kg once daily as an initial dose is recommended)<br>*Hemodialysis, intermittent (thrice weekly)*: Dialyzable (45% removed |

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| | during 8 hours of hemodialysis): Initial: Administer 50% to 100% of the indication-specific dose; if the initial dose is a dose range then it is recommended to begin with the lowest end of the dose range (eg, if the usual dose is 2 to 3 mg/kg once daily then administering 50% to 100% of 2 mg/kg once daily as an initial dose is recommended) (Ref). When scheduled dose falls on a dialysis day, administer after hemodialysis. If not administered after hemodialysis, provide a 50% supplemental dose<br>*Peritoneal dialysis*: Initial: Administer 50% to 100% of the indication-specific dose. If the initial dose is a dose range then it is recommended to begin with the lowest end of the dose range (eg, if the usual dose is 2 to 3 mg/kg once daily then administering 50% to 100% of 2 mg/kg once daily as an initial dose is recommended)<br>*CRRT*: Drug clearance is dependent on the effluent flow rate, filter type, and method of renal replacement. Recommendations are based on high-flux dialyzers and effluent flow rates of 20 to 25 mL/kg/hour (or ~1,500 to 3,000 mL/hour) unless otherwise noted. Close monitoring of response and adverse reactions (eg, hematologic toxicity) due to drug accumulation is important.<br>**Initial**: Administer 75% to 100% of the indication-specific dose. If the initial dose is a dose range then it is recommended to begin with the lowest end of the dose range (eg, if the usual dose is 2 to 3 mg/kg once daily then administering 75% to 100% of 2 mg/kg |

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| | once daily as an initial dose is recommended)<br>*PIRRT (eg, sustained, low-efficiency diafiltration*): Drug clearance is dependent on the effluent flow rate, filter type, and method of renal replacement. Appropriate dosing requires consideration of adequate drug concentrations (eg, site of infection) and consideration of initial loading doses. Close monitoring of response and adverse reactions (eg, hematologic toxicity) due to drug accumulation is important.<br>**Initial**: Administer 75% to 100% of the indication-specific dose. Administer the dose after PIRRT therapy ends on PIRRT days. If the initial dose is a dose range then it is recommended to begin with the lowest end of the dose range (eg, if the usual dose is 2 to 3 mg/kg once daily then administering 75% to 100% of 2 mg/kg once daily as an initial dose is recommended)<br>**Hepatic Impairment: Adult**<br>There are no dosage adjustments provided in the manufacturer's labeling.<br>**Adjustment for Toxicity: Adult**<br>*Rapid WBC count decrease, persistently low WBC count, or serious infection*: Reduce dose or temporarily withhold treatment.<br>*Severe toxicity (hematologic or other) in kidney transplantation*: May require discontinuation.<br>*Hepatic sinusoidal obstruction syndrome (SOS; veno-occlusive disease*): Permanently discontinue.<br>*Rheumatoid arthritis*: Leukopenia and thrombocytopenia: Consider a 50% dose reduction or discontinuation; |

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| | permanently discontinue for persistent cytopenias |
| **Prescribing edits** | ST, MD |
| **AGE (Age Edit):** | N/A |
| **CU (Concurrent Use Edit):** | N/A |
| **G (Gender Edit):** | N/A |
| **MD (Physician Specialty Edit):** | Only physicians experienced in immunosuppressive therapy and hematology should prescribe Azathioprine. |
| **PA (Prior Authorization):** | N/A |
| **QL (Quantity Limit):** | N/A |
| **ST (Step Therapy):** | This drug is recommended as an alternative immunomodulatory option for recurrent or refractory iTTP patients and pregnant women |
| **EU (Emergency Use Only):** | N/A |
| **PE (Protocol Edit):** | N/A |
| **SAFETY** | |
| **Main Adverse Drug Reactions (most common and most serious)** | **Most common:**<br>- GI effects (nausea, vomiting, diarrhea)<br>- Hematologic toxicity (leukopenia, thrombocytopenia, and anemias, including macrocytic anemia and/or pancytopenia)<br>- Infections (bacterial infections, viral infections, fungal infections, protozoal infections, and opportunistic infections; JC virus infection resulting in progressive multifocal leukoencephalopathy, cytomegalovirus (CMV) disease, herpes simplex virus infection, human papillomavirus infection, and reactivation of hepatitis B and tuberculosis)<br>- Liver dysfunction |

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| | - Malignancy (Malignancies reported have included malignant lymphoma, hepatosplenic T-cell lymphoma (HSTCL), hemophagocytic lymphohistiocytosis (HLH), acute myelocytic leukemia, myelodysplastic syndrome, and malignant neoplasm of skin, among others)<br>- Pancreatitis |
| **Drug Interactions*** | **<u>Category X:</u>**<br>• Abrocitinib<br>• Baricitinib<br>• BCG (Intravesical)<br>• BCG products<br>• Brivudine<br>• Cladribine<br>• Dengue Tetravalent Vaccine (Live)<br>• Deucravacitinib<br>• Dipyrone<br>• Febuxostat<br>• Fexinidazole<br>• Filgotinib<br>• Mercaptopurine<br>• Mumps- Rubella- or Varicella-Containing Live Vaccines<br>• Nadofaragene Firadenovec<br>• Natalizumab<br>• Pimecrolimus<br>• Poliovirus Vaccine (Live/Trivalent/Oral)<br>• Ritlecitinib<br>• Ruxolitinib (Topical)<br>• Tacrolimus (Topical)<br>• Talimogene Laherparepvec<br>• Tertomotide<br>• Tofacitinib<br>• Typhoid Vaccine |

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| | • Upadacitinib<br>• Vaccines (Live)<br>• Yellow Fever Vaccine |
| **Special Population** | N/A |
| **Pregnancy** | Azathioprine crosses the placenta. |
| **Lactation** | The azathioprine metabolite 6-mercaptopurine (6-MP) is present in breast milk.<br>Recommendations for breastfeeding during azathioprine therapy vary. Due to the potential for serious adverse reactions in the infant, breastfeeding is not recommended by the manufacturer. The World Health Organization also recommends breastfeeding be avoided during maternal treatment |
| **Contraindications** | Hypersensitivity to azathioprine or any component of the formulation; pregnancy (in patients with rheumatoid arthritis [see Pregnancy Considerations]); patients with rheumatoid arthritis and a history of treatment with alkylating agents (eg, cyclophosphamide, chlorambucil, melphalan) may have a prohibitive risk of malignancy with azathioprine treatment<br>Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information. |
| **Monitoring Requirements** | CBC with differential and platelets (weekly during first month, twice monthly for months 2 and 3, then monthly thereafter; monitor more frequently with dosage modifications or as clinically indicated), total bilirubin, LFTs (every 3 months), CrCl, monitor for signs/symptoms of infection and |

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| | malignancy (eg, splenomegaly, hepatomegaly, abdominal pain, persistent fever, night sweats, weight loss). Patients taking azathioprine for a prolonged time period should avoid sun exposure and be monitored for skin cancer regularly. |
| **Precautions** | Hepatic impairment: Use with caution in patients with hepatic impairment. Renal impairment: Use with caution in patients with renal impairment. |
| **Black Box Warning** | Malignancy (Reports of malignancy include post-transplant lymphoma and hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease) |
| **REMS** | N/A |

## HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Thrombotic Thrombocytopenic Purpura (TTP) treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Azathioprine.**

**Table 21.** Azathioprine HTA Analysis

| MEDICATION | AGENCY | DATE – HTA RECOMMENDATION |
|---|---|---|
| **Azathioprine** | NICE | N/A |
| | CADTH | N/A |
| | HAS[21] | **Positive** recommendation for the use of azathioprine in idiopathic thrombocytopenic purpura |
| | IQWIG | N/A |
| | PBAC | N/A |

**CONCLUSION STATEMENT- Azathioprine**

This drug is recommended as an alternative immunomodulatory option for recurrent or refractory iTTP patients and pregnant women. This drug is given as Oral: 1 to 2 mg/kg/day. Initial response is observed at 30 to 90 days; may take up to 6 months for peak response; maximum dose is 150 mg/day. Only physicians experienced in immunosuppressive therapy and hematology should prescribe Azathioprine. There are no HTA recommendations regarding the use of azathioprine in TTP other than the positive recommendation from HAS. Limitations for the use of Azathioprine include malignancy.

## 2.3 Anti-Neoplastic Agents

### 2.3.1 Cyclophosphamide

Information on Cyclophosphamide is detailed in the table below[14]

**Table 22.** Cyclophosphamide Drug Information

| **SCIENTIFIC NAME CYCLOPHOSPHAMIDE** | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA** | No |
| **US FDA** | No |
| **EMA** | No |
| **MHRA** | No |
| **PMDA** | Off-label |
| **Indication (ICD-10)** | M31.1 |
| **Drug Class** | Antineoplastic, Alkylating Agent, Antirheumatic, Immunosuppressant |
| **Drug Sub-class** | Nitrogen Mustard |
| **ATC Code** | L01AA01 |
| **Pharmacological Class (ASHP)** | Antineoplastic Agent |
| **DRUG INFORMATION** | |
| **Dosage Form** | Film-coated tablet, Powder for solution for injection |
| **Route of Administration** | IV use, Oral use |
| **Dose (Adult) [DDD]*** | 500 mg/m2 administered once daily over 2 hours. |

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| | This regimen is restricted to a single dose, as multiple doses may cause bone marrow suppression. |
| **Maximum Daily Dose Adults** | Maximum dose has not been established; some experts do not exceed 1,000 mg/dose IV. Do not exceed 150 mg/day oral. |
| **Dose (pediatrics)** | N/A |
| **Maximum Daily Dose Pediatrics** | N/A |
| **Adjustment** | CrCl 10 to 29 mL/minute: Administer 75% or 100% of PO normal dose.<br>CrCl <10 mL/minute: Administer 50%, 75%, or 100% of PO normal dose.<br>IV: Shorter, low-dose regimen (500 mg IV once every 2 weeks for 6 doses): No dosage adjustment necessary.<br>IV: Longer, high-dose regimen (500 to 1,000 mg/m2 IV pulses): CrCl <30 mL/minute: Reduce initial dose to 500 mg/m2<br>Hemodialysis, intermittent (thrice weekly): Moderately dialyzable (20% to 50% removal based on limited data with low-flux dialyzers): Administer 50% or 75% of the normal dose. On dialysis days, administer after hemodialysis, allowing at least 12 hours before the next hemodialysis session.<br>Peritoneal dialysis: Administer 75% of the normal dose. If possible, allow at least 12 hours before next peritoneal dialysis exchange.<br>CRRT: Administer 100% of the normal dose.<br>Hepatic adjustment: no dosage adjustments provided in the manufacturer's labeling. Floyd 2006 has recommended: Serum bilirubin 3.1 to 5 mg/dL or transaminases >3 times ULN: |

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| | Administer 75% of dose. Serum bilirubin >5 mg/dL: Avoid use. |
| **Prescribing edits** | QL, MD, ST, CU |
| **AGE (Age Edit):** | N/A |
| **CU (Concurrent Use Edit):** | To be given in combination with antiemetics. |
| **G (Gender Edit):** | N/A |
| **MD (Physician Specialty Edit):** | Only physicians experienced in immunosuppressive therapy and hematology should prescribe Cyclophosphamide. |
| **PA (Prior Authorization):** | N/A |
| **QL (Quantity Limit):** | This regimen is restricted to a single dose, as multiple doses may cause bone marrow suppression. |
| **ST (Step Therapy):** | This drug is recommended as an alternative option in patients with refractory or relapsing TTP |
| **EU (Emergency Use Only):** | N/A |
| **PE (Protocol Edit):** | N/A |
| **SAFETY** | |
| **Main Adverse Drug Reactions (most common and most serious)** | **Most common:** leukopenia, neutropenia, anemia, arrythmias and pericarditis.<br>**Most serious:** Bone marrow suppression and infection,<br>Cardiotoxicity,<br>Hemorrhagic cystitis,<br>Hepatotoxicity,<br>Pulmonary toxicity,<br>Second primary malignancy |
| **Drug Interactions*** | **Category X:**<br>• Abrocitinib<br>• Adenovirus (Types 4, 7) Vaccine Depends on International labeling<br>• Baricitinib<br>• BCG (Intravesical) (Immunization)<br>• Brivudine [INT] |

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| | • Cholera Vaccine Depends on International labeling<br>• Cladribine<br>• Dengue Tetravalent Vaccine (Live)<br>• Deucravacitinib<br>• Dipyrone<br>• Ebola Zaire Vaccine (Live) Depends on International labeling<br>• Etanercept<br>• Fexinidazole<br>• Filgotinib<br>• Influenza Virus Vaccine (Live/Attenuated) Depends on International labeling<br>• Japanese Encephalitis Virus Vaccine (Live/Attenuated) Depends on International labeling<br>• Measles, Mumps, and Rubella Virus Vaccine<br>• Measles, Mumps, Rubella, and Varicella Virus Vaccine<br>• Mumps Virus Vaccine Depends on International labeling<br>• Mumps Virus Vaccine<br>• Nadofaragene Firadenovec<br>• Natalizumab<br>• Pimecrolimus<br>• Poliovirus Vaccine (Live/Bivalent/Oral) Depends on International labeling<br>• Poliovirus Vaccine (Live/Trivalent/Oral)<br>• Rotavirus Vaccine Depends on International labeling<br>• Ruxolitinib (Topical)<br>• Smallpox Vaccine Live Depends on International labeling<br>• Tacrolimus (Topical)<br>• Talimogene Laherparepvec<br>• Tertomotide<br>• Tofacitinib |

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| | • Typhoid Vaccine<br>• Upadacitinib<br>• Varicella Virus Vaccine<br>• Voclosporin<br>• Yellow Fever Vaccine<br>• Zoster Vaccine (Live/Attenuated)<br>Depends on International labeling. |
| **Special Population** | Dosing adjustment for toxicity: Infants, Children, and Adolescents: Hematologic toxicity: May require dose reduction or treatment interruption.<br>Hemorrhagic cystitis, severe: Discontinue treatment.<br>Older Adult Considerations<br>Toxicity to immunosuppressives is increased in the elderly. Start with lowest recommended adult doses. Signs of infection, such as fever and elevated WBC, may not occur. Lethargy and confusion may be more prominent signs of infection; adjust dose for renal function. |
| **Pregnancy** | Cyclophosphamide crosses the placenta and can be detected in amniotic fluid. In patients with life- or organ-threatening maternal disease, cyclophosphamide may be used in the second or third trimesters only when an alternative therapy is not available |
| **Lactation** | Cyclophosphamide and its metabolites are present in breast milk. Cyclophosphamide is not recommended for use in breastfeeding mothers with autoimmune and systemic inflammatory diseases. breastfeeding is not recommended by the manufacturer during therapy and for 1 week after the last cyclophosphamide dose. Others recommend breastfeeding be avoided |

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| | for at least 6 weeks after the last dose of cyclophosphamide |
| **Contraindications** | History of severe hypersensitivity to cyclophosphamide, its metabolites, or any component of the formulation; urinary outflow obstruction.<br>Canadian labeling: Additional contraindications (not in the US labeling): Severe myelosuppression, severe renal or hepatic impairment, active infection (especially varicella zoster), severe immunosuppression. |
| **Monitoring Requirements** | Obtain CBC with differential and platelets, serum electrolytes, BUN, serum creatinine, and urinalysis. Dosage in the obese should be weight based. Premedicate with an antiemetic and MESNA. Assess for signs and symptoms of hemorrhagic cystitis, renal toxicity, pulmonary toxicity, cardiac toxicity, and liver toxicity. |
| **Precautions** | Use with caution in patients with hepatic or renal impairment.<br>Hypersensitivity: Possible cross-sensitivity with other alkylating agents may occur.<br>Some cyclophosphamide injection dosage forms may contain alcohol. The alcohol content (in some dosage forms) may affect the CNS and impair the ability to drive or operate machinery. |
| **Black Box Warning** | N/A |
| **REMS** | N/A |

## HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Thrombotic Thrombocytopenic Purpura (TTP) treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG),

and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Cyclophosphamide.**

**Table 23.** Cyclophosphamide HTA Analysis

| MEDICATION | AGENCY | DATE – HTA RECOMMENDATION |
|---|---|---|
| **Cyclophosphamide** | NICE | N/A |
| | CADTH | N/A |
| | HAS | N/A |
| | IQWIG | N/A |
| | PBAC | N/A |

**CONCLUSION STATEMENT- Cyclophosphamide**

This drug is recommended as an alternative option in patients with refractory or relapsing iTTP. Only physicians experienced in immunosuppressive therapy and hematology should prescribe Cyclophosphamide. Cyclophosphamide 500 mg/m2 administered once daily over 2 hours. This regimen is restricted to a single dose, as multiple doses may cause bone marrow suppression. There are no HTA recommendations regarding its use in TTP. Limitations for the use of Cyclophosphamide include bone marrow suppression, cardiotoxicity, and hepatotoxicity.

### 2.3.2 Vincristine

The table below showcases the drug information related to Vincristine[14]:

**Table 24.** Vincristine Drug Information

| Scientific Name<br>Vincristine | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA approved Indication** | Yes |
| **FDA approved** | No |
| **EMA approved** | No |
| **MHRA approved** | Yes |
| **PMDA approved** | Yes, Off label |
| **Indication (ICD-10)** | M31.1 |
| **Drug Class** | Antineoplastic agent |
| **Drug Sub-class** | Antimicrotubular, Vinca Alkaloid |
| **ATC Code** | L01CA02 |

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| **Pharmacological Class (ASHP)** | Antineoplastic Agents |
| **DRUG INFORMATION** | |
| **Dosage Form** | Solution for injection |
| **Route of Administration** | Intravenous |
| **Dose (Adult) [DDD]** | Vincristine 1 mg/m2 is administered IV at a slow infusion rate[7].<br>This regimen is restricted to a single dose, as multiple doses may cause neurotoxicity and bone marrow suppression[7].<br><br>Other primary literature reported vincristine as administered intravenously 1 or 2 mg on day 1, followed by 1 mg on days 4 and 7 following TPE. A second course was given after a 1-week interval[22]. |
| **Dose (Pediatrics)** | N/A |
| **Adjustment** | Hepatic Impairment (Adult/Pediatric):<br>- Serum bilirubin 1.5 to 3 mg/dL or transaminases 2 to 3 times ULN or alkaline phosphatase increased: Administer 50% of dose. |
| **Prescribing edits** | MD, ST, QL, CU |
| **AGE (Age Edit)** | N/A |
| **CU (Concurrent Use)** | Can be used in combination with corticosteroids and/or plasma exchange |
| **G (Gender Edit)** | N/A |
| **MD (Physician Specialty Edit)** | To be prescribed by a hematologist |
| **PA (Prior Authorization)** | N/A |
| **QL (Quantity Limit)** | Maximum of 2 mg per dose |
| **ST (Step Therapy)** | This drug is recommended in relapsed/ refractory patients |
| **EU (Emergency Use Only)** | N/A |
| **PE (Protocol Edit)** | N/A |
| **Maximum Daily Dose Adults** | 2 mg |
| **Maximum Daily Dose Pediatrics** | 2 mg |
| **SAFETY** | |

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| **Main Adverse Drug Reactions (Most common and most serious)** | - Most common: Hypertension, hypotension, alopecia, dehydration, hyperuricemia, weight loss, abdominal cramps, anorexia, constipation (may involve upper colon fecal impaction), diarrhea, intestinal necrosis, intestinal perforation, nausea, oral mucosa ulcer, paralytic ileus, vomiting, bladder dysfunction (atony), dysuria, leukopenia, abnormal gait, cranial nerve disorder, decreased deep tendon reflex, headache, neuritic pain, paresthesia, sensorimotor neuropathy, amyotrophy, foot-drop), oliguria, fever<br>- Most serious: Ataxia, paralysis, acute respiratory distress syndrome, uric acid nephropathy |
| **Drug Interactions*** | - Risk X: Fexinidazole, Fusidic Acid (Systemic)<br>- Risk D: CYP3A4 Inhibitors (Strong), Lenograstim, Lipegfilgrastim, Palifermin |
| **Special Population** | N/A |
| **Pregnancy** | Pregnancy Category D: Not used in pregnancy |
| **Lactation** | It is not known if vincristine is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, the decision to discontinue vincristine or to discontinue breastfeeding should consider the benefits of treatment to the mother. |
| **Contraindications** | Patients with the demyelinating form of Charcot-Marie-Tooth syndrome |
| **Monitoring Requirements** | - Serum electrolytes (sodium)<br>- Hepatic function tests<br>- CBC with differential, serum uric acid. |

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| | - Monitor for signs or symptoms of hepatic sinusoidal obstruction syndrome, including bilirubin >1.4 mg/dL, unexplained weight gain, ascites, hepatomegaly, or unexplained right upper quadrant pain.<br>- Monitor infusion site.<br>- Perform neurologic examination, monitor for constipation/ileus and for signs/symptoms of peripheral neuropathy. |
| **Precautions** | - Extravasation<br>- Gastrointestinal toxicity<br>- Neurotoxicity<br>- Respiratory effects<br>- Uric acid nephropathy<br>- Hepatic impairment: Use with caution<br>- **For IV administration only; fatal if given by other routes** |
| **Black Box Warning** | - Experienced physician<br>- Extravasation<br>- Appropriate administration |
| **REMS** | N/A |

**HEALTH TECHNOLOGY ASSESSMENT (HTA)**

The table below lists the HTA reviews and recommendations of Thrombotic Thrombocytopenic Purpura (TTP) treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Vincristine.**

**Table 25.** Vincristine HTA Analysis

| MEDICATION | AGENCY | DATE – HTA RECOMMENDATION |
|---|---|---|
| **Vincristine** | NICE | N/A |
| | CADTH | N/A |
| | HAS[12] | **February 16, 2006**<br>The actual benefit of ONCOVIN is **moderate** in idiopathic thrombocytopenic purpura resistant to usual treatments |
| | IQWIG | N/A |
| | PBAC | N/A |

**CONCLUSION STATEMENT- Vincristine**

This drug is recommended as an alternative option for relapsed or refractory TTP. This drug is given as 1 mg/m2 is administered IV once daily at a slow infusion rate. This regimen is restricted to a single dose, as multiple doses may cause neurotoxicity and bone marrow suppression. Only physicians experienced in oncology and hematology should prescribe Vincristine. There are no HTA recommendations regarding the use of Vincristine in TTP other than the moderate recommendation from HAS. Limitations for the use of Vincristine include neurotoxicity, uric acid nephropathy, extravasation, hepatic impairment, GI toxicity, respiratory effects, and route of administration.

### 2.3.3 Bortezomib

The table below showcases the drug information related to Bortezomib[14]:

**Table 26.** Bortezomib Drug Information

| **Scientific Name**<br>**Bortezomib** | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA approved Indication** | No |
| **FDA approved** | No |
| **EMA approved** | No |
| **MHRA approved** | No |
| **PMDA approved** | No |
| **Indication (ICD-10)** | M31.1 |
| **Drug Class** | Antineoplastic agent |

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| **Drug Sub-class** | Proteasome Inhibitor |
| **ATC Code** | L01XX32 |
| **Pharmacological Class (ASHP)** | Antineoplastic Agents |
| **DRUG INFORMATION** | |
| **Dosage Form** | Solution for injection, powder for solution for injection |
| **Route of Administration** | Intravenous, Subcutaneous |
| **Dose (Adult) [DDD]** | **Limited data available**:<br>ASH publications[23]: 4 doses of 2mg bortezomib (SC) given 3 days apart.<br>Velcade package information[24]: The recommended starting dose of VELCADE is 1.3 mg/m2. VELCADE is administered intravenously at a concentration of 1 mg/mL, or subcutaneously at a concentration of 2.5 mg/mL |
| **Dose (Pediatrics)** | N/A |
| **Adjustment** | - Kidney impairment: no dosage adjustment is necessary<br>- Hepatic impairment:<br>*Hepatic impairment prior to treatment initiation:*<br>Mild impairment (bilirubin ≤ ULN and AST >ULN or bilirubin >1 to 1.5 times ULN and any AST): No initial dose adjustment is necessary.<br>Moderate (bilirubin >1.5 to 3 times ULN and any AST) and severe impairment (bilirubin >3 times ULN and any AST): Reduce initial dose to 0.7 mg/m2 in the first cycle; based on patient tolerance, may consider dose escalation to 1 mg/m2 or further dose reduction to 0.5 mg/m2 in subsequent cycles.<br>*Hepatotoxicity during treatment*:<br>Interrupt bortezomib treatment (to assess reversibility) if acute liver failure, hepatitis, increased |

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| | transaminases, and/or hyperbilirubinemia occur; information on bortezomib rechallenge is limited. |
| **Prescribing edits** | MD, ST, AGE, CU |
| **AGE (Age Edit)** | Bortezomib is not approved for a pediatric indication because no clinical benefit was demonstrated in the clinical trial in 2015[25]. |
| **CU (Concurrent Use)** | Can be used in combination with corticosteroids |
| **G (Gender Edit)** | N/A |
| **MD (Physician Specialty Edit)** | To be prescribed by an oncologist |
| **PA (Prior Authorization)** | N/A |
| **QL (Quantity Limit)** | N/A |
| **ST (Step Therapy)** | This drug is recommended in relapsed/ refractory patients |
| **EU (Emergency Use Only)** | N/A |
| **PE (Protocol Edit)** | N/A |
| **Maximum Daily Dose Adults** | N/A |
| **Maximum Daily Dose Pediatrics** | N/A |
| **SAFETY** | |
| **Main Adverse Drug Reactions (Most common and most serious)** | **>10%:**<br>- Dermatologic: Skin rash<br>- Gastrointestinal: Abdominal pain, anorexia, constipation, decreased appetite, diarrhea, nausea, vomiting<br>- Hematologic & oncologic: Anemia, leukopenia, neutropenia, thrombocytopenia<br>- Infection: Herpes zoster infection<br>- Nervous system: Dizziness, fatigue, headache, malaise, neuralgia, paresthesia, peripheral neuropathy (including peripheral motor neuropathy and peripheral sensory neuropathy)<br>- Neuromuscular & skeletal: Asthenia<br>- Respiratory: Dyspnea |

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| | - Miscellaneous: Fever |
| **Drug Interactions*** | **CATEGORY X interactions:**<br>- BCG (Intravesical)<br>- Bromperidol<br>- Cladribine<br>- CYP3A4 Inducers (Strong)<br>- Dipyrone<br>- Fexinidazole<br>- Fusidic Acid (Systemic) |
| **Special Population** | N/A |
| **Pregnancy** | Based on the mechanism of action and on findings in animal reproduction studies, bortezomib may cause fetal harm if administered during pregnancy. |
| **Lactation** | It is not known if bortezomib is present in breast milk. The manufacturer recommends lactating patients avoid breastfeeding during and for 2 months following bortezomib treatment. |
| **Contraindications** | Hypersensitivity (excluding local reactions) to bortezomib, boron, boric acid (generic product), glycine (some generics), mannitol (Velcade, some generics), or any component of the formulations; administration via the intrathecal route. |
| **Monitoring Requirements** | CBC with differential and platelets (monitor frequently throughout therapy); liver function tests (in patients with existing hepatic impairment); renal function. Monitor blood glucose (in patients with diabetes). Verify pregnancy status prior to therapy initiation in patients who could become pregnant. Monitor BP. Monitor for signs/symptoms of peripheral neuropathy (consider SUBQ administration in patients with preexisting or at high risk for peripheral neuropathy), dehydration, hypotension |

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| | (use with caution in patients with dehydration, history of syncope, or taking medications associated with hypotension), posterior reversible leukoencephalopathy syndrome, progressive multifocal leukoencephalopathy, tumor lysis syndrome, or hyper-/hypoglycemia. Monitor baseline chest x-ray and then periodic pulmonary function testing (with new or worsening pulmonary symptoms). Monitor closely in patients with risk factors for heart failure or existing heart disease.<br>The American Society of Clinical Oncology hepatitis B virus (HBV) screening and management provisional clinical opinion recommends HBV screening with hepatitis B surface antigen, hepatitis B core antibody, total Ig or IgG, and antibody to hepatitis B surface antigen prior to beginning (or at the beginning of) systemic anticancer therapy; do not delay treatment for screening/results. Detection of chronic or past HBV infection requires a risk assessment to determine antiviral prophylaxis requirements, monitoring, and follow-up.<br>Cardiovascular monitoring: Comprehensive assessment prior to treatment including a history and physical examination, screening for cardiovascular disease risk factors such as hypertension, diabetes, dyslipidemia, obesity, and smoking. Assess BP at baseline and each clinical visit (also consider weekly home monitoring for initial 3 months, then monthly thereafter); assess natriuretic peptide at baseline for high and very high-risk |

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| | patients and consider at each cycle for the first 6 cycles; consider checking natriuretic peptide at baseline for low- and moderate-risk patients; obtain a baseline echocardiography in all patients. |
| **Precautions** | **Bone marrow suppression**: Hematologic toxicity, including grade 3 and 4 neutropenia and thrombocytopenia may occur; risk is increased in patients with pretreatment platelet counts <75,000/mm3. Nadirs generally occur following the last dose of a cycle and recover prior to the next cycle. Hemorrhage (GI and intracerebral) due to low platelet count has been observed. Neutropenic fever has been observed.<br>**Cardiovascular effects**: Acute development or exacerbation of HF and new onset decreased left ventricular ejection fraction (LVEF) have been reported with bortezomib; some cases have occurred in patients without risk factors for HF and/or decreased LVEF. Isolated case of QTc prolongation have been reported with bortezomib.<br>**GI effects**: Nausea, vomiting, diarrhea, constipation, or ileus may occur.<br>**Hepatotoxicity**: Acute liver failure has been reported (rarely) in patients receiving multiple concomitant medications and with serious underlying conditions. Hepatitis, transaminase increases, and hyperbilirubinemia have also been reported. Limited data exist for patients that have been rechallenged.<br>**Herpes reactivation**: Herpes (zoster and simplex) reactivation has been reported with bortezomib. |

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| | **Hypersensitivity**: Anaphylactic reaction, drug hypersensitivity, immune complex mediated hypersensitivity, angioedema, and laryngeal edema have been reported with bortezomib.<br>**Hypotension**: Bortezomib may cause hypotension (including postural and orthostatic).<br>**Peripheral neuropathy**: Bortezomib may cause or worsen peripheral neuropathy (usually sensory but may be mixed sensorimotor); risk may be increased with previous use of neurotoxic agents or preexisting peripheral neuropathy (in patients with preexisting neuropathy, use only after risk versus benefit assessment). The incidence of grades 2 and 3 peripheral neuropathy may be lower with SUBQ route (compared to IV). Most patients with ≥ grade 2 peripheral neuropathy have improvement in or resolution of symptoms with dose adjustments or discontinuation. In a study of patients ≥65 years of age receiving a weekly bortezomib schedule with combination chemotherapy, the incidence of peripheral neuropathy was significantly reduced without an effect on outcome.<br>**Posterior reversible leukoencephalopathy syndrome**: Posterior reversible leukoencephalopathy syndrome (PRES, formerly RPLS) has been reported (rarely). Symptoms of PRES include confusion, headache, hypertension, lethargy, seizure, blindness and/or other vision, or neurologic disturbances.<br>**Progressive multifocal leukoencephalopathy**: Progressive multifocal leukoencephalopathy has |

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| | been rarely observed; symptoms may include confusion, loss of balance, vision disturbances, reduced strength, or weakness in an arm/leg.<br>**Pulmonary toxicity**: Pulmonary disorders (some fatal) including pneumonitis, interstitial pneumonia, lung infiltrates, and acute respiratory distress syndrome (ARDS) have been reported. Pulmonary hypertension (without left heart failure or significant pulmonary disease) has been reported rarely.<br>**Thrombotic microangiopathy**: Cases (some fatal) of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, have been reported.<br>**Tumor lysis syndrome**: Tumor lysis syndrome has been reported with bortezomib; risk is increased in patients with high tumor burden prior to treatment. |
| **Black Box Warning** | N/A |
| **REMS** | N/A |

**HEALTH TECHNOLOGY ASSESSMENT (HTA)**

The table below lists the HTA reviews and recommendations of Thrombotic Thrombocytopenic Purpura (TTP) treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Bortezomib.**

**Table 27.** Bortezomib HTA Analysis

| MEDICATION | AGENCY | DATE – HTA RECOMMENDATION |
|---|---|---|
| **Bortezomib** | NICE | N/A |
| | CADTH | N/A |
| | HAS | N/A |
| | IQWIG | N/A |
| | PBAC | N/A |

**CONCLUSION STATEMENT- Bortezomib**

Bortezomib is recommended as an alternative option for relapsed or refractory TTP. The recommended starting dose of this drug is 1.3 mg/m2. Bortezomib is administered intravenously at a concentration of 1 mg/mL, or subcutaneously at a concentration of 2.5 mg/mL. Only physicians experienced in oncology and hematology should prescribe Bortezomib. There are no HTA recommendations regarding the use of Bortezomib in TTP. Limitations for the use of Bortezomib include bone marrow suppression, cardiovascular and GI effects, pulmonary toxicity and hepatoxicity, herpes reactivation, hypersensitivity, peripheral neuropathy, progressive multifocal leukoencephalopathy, Posterior reversible leukoencephalopathy syndrome, Thrombotic microangiopathy, and Tumor lysis syndrome.

## 2.4 Blood Thinners

### 2.4.1 Aspirin

Aspirin is an antiplatelet used to decrease the risk of blood clot. The detailed drug information on aspirin place in therapy, pharmacological information, dose and administration and safety profile are represented in the table below:[14]

**Table 28.** Aspirin Drug Information

| SCIENTIFIC NAME<br>ACETYL SALICYLIC ACID | |
|---|---|
| **SFDA Classification** | Over the counter (OTC) |
| **SFDA** | Yes, February 2021 |
| **US FDA** | Yes, February 2010 |
| **EMA** | Yes |
| **MHRA** | Yes, October 2009 |
| **PMDA** | Yes, January 2014 |

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| **Indication (ICD-10)** | M31.1 |
| **Drug Class** | Other antiplatelets, analgesics and antipyretics |
| **Drug Sub-class** | Salicylic acid and derivatives |
| **ATC Code** | N02BA01 |
| **Pharmacological Class (ASHP)** | Antiplatelet, Non-opioid analgesic - Irreversible COX1/COX2 Inhibitor |
| **DRUG INFORMATION** | |
| **Dosage Form** | Enteric-coated tablets, tablet |
| **Route of Administration** | Oral |
| **Dose (Adult) [DDD]** | 75-100 mg/day |
| **Maximum Daily Dose Adults** | 325 mg |
| **Dose (pediatrics)** | Limited data available.<br>1-5 mg/kg/dose once daily. |
| **Maximum Daily Dose Pediatrics** | N/A |
| **Adjustment** | • Renal: No dose adjustment required<br>• Liver: Avoid use in severe liver disease |
| **Prescribing edits** | AGE, ST |
| **AGE (Age Edit)** | Aspirin should not be given to children aged under 16 unless on the advice of a physician. |
| **CU (Concurrent Use Edit)** | N/A |
| **G (Gender Edit)** | N/A |
| **MD (Physician Specialty Edit)** | N/A |
| **PA (Prior Authorization)** | N/A |
| **QL (Quantity Limit)** | N/A |
| **ST (Step Therapy)** | This drug is recommended as first line for thrombosis prevention along with LWMH therapy |
| **EU (Emergency Use Only)** | N/A |
| **PE (Protocol Edit)** | N/A |
| **SAFETY** | |
| **Main Adverse Drug Reactions (most common and most serious)** | • Cardiovascular: Cardiac arrhythmia, hypotension, tachycardia<br>• Endocrine & metabolic: Dehydration, hyperglycemia, hyperkalemia, |

| | |
|---|---|
| | hypoglycemia (children), increased thirst, metabolic acidosis<br>• Gastrointestinal: Abdominal pain, dyspepsia, gastrointestinal perforation, gastrointestinal ulcer, heartburn, nausea, vomiting<br>• Genitourinary: Postpartum hemorrhage, post-term pregnancy, prolonged labor, proteinuria, stillborn infant<br>• Hematologic & oncologic: Disorder of hemostatic components of blood, disseminated intravascular coagulation, hemorrhage, prolonged bleeding time, prolonged prothrombin time, thrombocytopenia<br>• Hepatic: Hepatitis, increased liver enzymes<br>• Nervous system: Agitation, brain edema, coma, confusion, dizziness, headache, hypothermia, lethargy, seizure<br>• Renal: Increased blood urea nitrogen, increased serum creatinine, interstitial nephritis, renal failure syndrome, renal insufficiency, renal papillary necrosis<br>• Respiratory: Hyperventilation, laryngeal edema, pulmonary edema, respiratory alkalosis, tachypnea<br>• Miscellaneous: Fever, low birth weight |
| **Drug Interactions*** | **<u>Category X:</u>**<br>Dexibuprofen, dexketoprofen, ketorolac, macimerolin, urokinase. |
| **Special Population** | N/A |
| **Pregnancy** | Crosses the placenta: risk vs benefits |
| **Lactation** | Risk vs benefits |
| **Contraindications** | Hypersensitivity |

| | |
|---|---|
| **Monitoring Requirements** | Hypersensitivity reactions |
| **Precautions** | • Bariatric surgeries<br>• Bleeding<br>• Hepatic impairment |
| **Black Box Warning** | N/A |
| **REMS*** | N/A |

## HEALTH TECHONOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of TTP treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The following HTA recommendations are for Aspirin.**

**Table 29.** Aspirin HTA Analysis

| Medication | Agency | Date – HTA Recommendation |
|---|---|---|
| **Aspirin** | NICE | Not available |
| | CADTH | Not available |
| | HAS | Not available |
| | IQWIG | Not available |
| | PBAC | Not available |

### CONCLUSION STATEMENT- ASPIRIN

**Aspirin is considered as a first line for thrombosis prevention** and should be initiated when thrombocytopenia resolves. While there is no HTA data regarding its use for the prevention of thrombosis, aspirin has been marketed worldwide for decades, and multiple generic options are available, leading to a low cost of treatment.

### 2.4.2 Enoxaparin

The table below showcases the drug information related to Enoxaparin[14]:

**Table 30.** Enoxaparin Drug Information

| **SCIENTIFIC NAME**<br>**Enoxaparin** | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA** | Yes |
| **US FDA** | Yes |
| **EMA** | Yes |
| **MHRA** | Yes |
| **PMDA** | Yes |
| **Indication (ICD-10)** | M31.1 |
| **Drug Class** | Anticoagulant |
| **Drug Sub-class** | Low Molecular Weight Heparin |
| **ATC Code** | B01AB05 |
| **Pharmacological Class (ASHP)** | N/A |
| **DRUG INFORMATION** | |
| **Dosage Form** | Solution for injection in pre-filled syringe, solution for injection |
| **Route of Administration** | IV, SC |
| **Dose (Adult) [DDD]** | 40 mg daily once platelets improve |
| **Maximum Daily Dose Adults*** | N/A |
| **Dose (pediatrics)** | Limited data available.<br>0.5-0.75 mg/kg/day every 12 hours |
| **Maximum Daily Dose Pediatrics** | N/A |
| **Adjustment** | • Renal:<br>CrCl <30 mL/minute: SUBQ: 30 mg once daily<br>• Liver: Avoid use in severe liver disease |
| **Prescribing edits*** | ST |
| **AGE (Age Edit)** | N/A |
| **CU (Concurrent Use Edit)** | N/A |
| **G (Gender Edit)** | N/A |
| **MD (Physician Specialty Edit)** | N/A |

| | |
|---|---|
| **PA (Prior Authorization)** | N/A |
| **QL (Quantity Limit)** | N/A |
| **ST (Step Therapy)** | LWMH are recommended as first line for prevention of thrombosis |
| **EU (Emergency Use Only)** | N/A |
| **PE (Protocol Edit)** | N/A |
| **SAFETY** | |
| **Main Adverse Drug Reactions (most common and most serious)** | • Hematologic & oncologic: Anemia<br>• Major bleeding: bleeding is partially reversible with the use of the antidote protamine<br>• Spinal or epidural hematomas<br>• Thrombocytopenia: Heparin-induced thrombocytopenia (HIT) and thrombosis in heparin-induced thrombocytopenia (HITT) have occurred, with some cases complicated by organ infarction, limb ischemia, and/or death. Low platelet counts from acute HIT are reversible upon enoxaparin discontinuation and initiation of appropriate interventions |
| **Drug Interactions*** | **<u>Category X:</u>**<br>- Apixaban<br>- Dabigatran Etexilate<br>- Defibrotide<br>- Edoxaban<br>- Hemin<br>- MiFEPRIStone<br>- Omacetaxine<br>- Rivaroxaban<br>- Urokinase<br>- Vorapaxar |
| **Special Population** | **Older adul**t: Use with caution in older patients; delayed elimination may occur. Dosage alteration/adjustment may be required (eg, omission of IV bolus and reduced treatment dose in |

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| | acute STEMI in patients ≥75 years of age).<br>**Low weight patients**: Risk of bleeding may be increased in women <45 kg and in men <57 kg.<br>**Elective surgery/procedure**: In patients receiving bridging anticoagulation with therapeutic dose enoxaparin, the last dose should be administered ~24 hours prior to the surgery/procedure. For patients on a twice-daily regimen, administer 1 dose in the morning the day before surgery. For patients on a once-daily regimen, administer 50% of the dose in the morning the day before surgery. Reinitiate therapy ≥24 hours after the surgery/procedure when bleeding risk is acceptable |
| **Pregnancy** | Low-molecular-weight heparin (LMWH) does not cross the placenta |
| **Lactation** | It is not known if enoxaparin is present in breast milk. |
| **Contraindications** | Known hypersensitivity to enoxaparin (eg, pruritus, urticaria, anaphylactic/anaphylactoid reactions), heparin, pork products, or any component of the formulation (including benzyl alcohol in multiple-dose vials); history of immune mediated heparin-induced thrombocytopenia (HIT) in the past 100 days or in the presence of circulating antibodies; active major bleeding |
| **Monitoring Requirements** | Hypersensitivity reactions, signs and symptoms of bleeding (Hb, Hct, Platelets), SrCr, |
| **Precautions** | **Bleeding**: Do not administer further doses until 6 to 8 hours after sheath removal; observe for signs of bleeding/hematoma formation. |

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| | **Hyperkalemia**: May rarely cause hyperkalemia possibly by suppressing aldosterone production. Most commonly occurs in patients with risk factors for the development of hyperkalemia (eg, kidney dysfunction, concomitant use of potassium-sparing diuretics or potassium supplements, hematoma in body tissues).<br>**Thrombocytopenia**: Use with extreme caution or avoid in patients with history of HIT. In patients with a history of HIT, use only if >100 days have elapsed since the prior HIT episode and no circulating antibodies are present (HIT may still occur in these patients; assess risk vs benefit and use only after non-heparin alternative treatments are considered). Discontinue therapy and consider alternative treatment if platelets are <100,000/mm3 and/or thrombosis develops. |
| **Black Box Warning** | Spinal/Epidural hematoma: Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary. Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis. |
| **REMS** | N/A |

**HEALTH TECHONOLOGY ASSESSMENT (HTA)**

The table below lists the HTA reviews and recommendations of TTP treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The HTA recommendations below are for Enoxaparin:**

**Table 31.** Enoxaparin HTA Analysis

| Medication | Agency | Date – HTA Recommendation |
|---|---|---|
| **Enoxaparin** | NICE | Not available |
| | CADTH | Not available |
| | HAS | Not available |
| | IQWIG | Not available |
| | PBAC | Not available |

**CONCLUSION STATEMENT- Enoxaparin**

**Enoxaparin is recommended as first line therapy for thrombosis prevention** and should be initiated when thrombocytopenia resolves. While there is no HTA data regarding its use for the prevention of thrombosis, LWMH has been marketed worldwide for decades, and multiple generic options are available, leading to a low cost of treatment.

## Section 3.0 Key Recommendations Synthesis

The key recommendations are listed below along with their respective levels of evidence:

- Fresh frozen plasma or cryodepleted plasma are used for plasma exchange. Until plasma exchange can be initiated, plasma infusion (15–30 ml/kg of body weight, daily) is used. In parallel, corticosteroids (e.g., prednisone) should be used for all patients, bortezomib in refractory patients, and vincristine in relapsed/ refractory patients[4].
- PEX should be started within 4 hours of admission and within of 8 hours of initial diagnosis[6].
- In parallel, clinicians recommend the use of corticosteroids (e.g., methylprednisolone and prednisolone) and mycophenolate mofetil in all patients, although ciclosporin may be used as an alternative to mycophenolate mofetil. Relapsed/refractory patients are treated with bortezomib[4].
- Acute phase – Corticosteroids (grade of recommendation: 1B)[7]:
    - Corticosteroids are administered either as pulse or high-dose therapy (no consensus regarding the superiority of either modality). Both modalities are used as off-label in Japan.

    - Lower doses should be considered in patients who are elderly or have diabetes mellitus or severe infections.
- The guidelines recommend the use of caplacizumab in addition to TPE and immunosuppression in confirmed aTTP episodes[8].
- Caplacizumab is approved by NICE for use in patients with[6]:
    - Acute acquired, immune TTP (with confirmed ADAMTS13 deficiency)
    - Age more than 12 years
    - Weight more than 40kg.
- Frontline addition of caplacizumab does not significantly reduce all-cause mortality compared with SOC alone, although it reduces refractory disease risk, shortens time to response, and improves exacerbation rates at the expense of increased relapse and bleeding risk[9].
- Monoclonal anti-CD20 therapy, such as rituximab, should be initiated within 3 days of acute iTTP admission (1B)[10].
- Acute phase - Rituximab (grade of recommendation: 2B)[7]
    - In Japan, rituximab is indicated for refractory or recurrent TTP only, and its use in the acute phase of TTP is not subject to national health insurance coverage. However, physicians may consider rituximab for the treatment of patients in the acute phase of iTTP
    - In patients undergoing plasma exchange, rituximab should be administered after the end of the plasma exchange session.
- In patients who have refractory iTTP or have severe ADAMTS13 deficiency despite anti-CD20 therapy, alternative immunosuppressive therapy should be considered (2B)[10].
- Refractory or early-relapse TTP: Splenectomy surgery (grade of recommendation: 2C) and high-dose immunoglobulin (grade of recommendation: 2C) were frequently administered to treat patients with refractory or recurrent TTP. These treatments have been superseded by rituximab therapy[7].
- Remission period: After the patient has achieved full remission, corticosteroids should be discontinued at the earliest opportunity based on ADAMTS13 activity and inhibitor titer measurements[7].
- Patients presenting for the first time with TTP in pregnancy should initially be treated as per iTTP with PEX and steroids (1A)[10].

- For pregnant women with iTTP refractory to PEX and steroids or who relapse, additional treatment options include ciclosporin, azathioprine and rituximab (2C)[10].
- In case of pregnant patients with iTTP and decreased plasma ADAMTS13 activity (< 10%) but with no clinical signs/symptoms: Prophylactic treatment over no prophylactic treatment (strong recommendation in the context of very low certainty evidence)[13].
- Pregnancy associated TTP: Steroids can be used until the results of ADAMTS13 antibodies are available. Rituximab has been used during pregnancy for a variety of autoimmune conditions but is reserved for severe or refractory immune mediated disease or when disease is life threatening and only after discussion with a consultant hematologist[6].
- For pregnant women with cTTP, regular SD-FFP replacement therapy should be given prophylactically to prevent clinical TTP relapse (1B)[10].
- In case of cTTP in remission: either plasma infusion or a watch and wait strategy and no use of factor VIII concentrate but a watch and wait strategy (conditional recommendation in the context of very low certainty evidence)[13].
- In case of pregnant patients with cTTP: Prophylactic treatment with plasma infusion over FVIII products for prophylaxis (conditional recommendation in the context of very low certainty evidence)[13].
- Congenital TTP: Current treatment consists of use of Octaplas infusions, or a virally inactivated intermediate purity factor VIII concentrate containing ADAMTS13 such as 8Y or virally inactivated FFP such as Octaplas. Frequency of treatment is variable; some patients require regular prophylactic therapy to maintain normal platelet counts whereas more mildly affected phenotypes may only require occasional treatment[6].
- Once platelet count has improved, clinicians use antithrombotic agents (i.e., aspirin and low-molecular-weight heparins)[4].
- All hospitalized/immobilized patients should receive thromboprophylaxis once platelet counts are ≥50 × 109/L, even when treated with caplacizumab (1B)[10].
- Aspirin, other antiplatelet drugs and LMWH should not routinely be given during caplacizumab treatment[6].
- Acute phase - Antiplatelet drugs (grade of recommendation: 2B)[7]
    - Concomitant use of aspirin and caplacizumab may increase the risk of bleeding and should be avoided.

- HIV-associated iTTP should be treated with HAART and plasma exchange/steroids/caplacizumab (1B)[10].

## Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of Thrombotic Thrombocytopenic Purpura.

These recommendations should be used to support and not supplant decisions in individual patient management.

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# Section 6.0 Appendices

## Appendix A. Prescribing Edits Definition

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

| Prescribing edits Tools | Description |
|---|---|
| **AGE (Age):** | Coverage may depend on patient age |
| **CU (Concurrent Use):** | Coverage may depend upon concurrent use of another drug |
| **G (Gender):** | Coverage may depend on patient gender |
| **MD (Physician Specialty):** | Coverage may depend on prescribing physician's specialty or board certification |
| **PA (Prior Authorization):** | Requires specific physician request process |
| **QL (Quantity Limits):** | Coverage may be limited to specific quantities per prescription and/or time period |
| **ST (Step Therapy):** | Coverage may depend on previous use of another drug |
| **EU (Emergency Use only):** | This drug status on Formulary is only for emergency use |
| **PE (Protocol Edit):** | Use of drug is dependent on protocol combination, doses and sequence of therapy |

## Appendix B. PubMed Search Methodology Terms

The following PubMed Search Methodology was opted:

| Query | Filters | Search Details | Results |
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| ((((((((((((((((((((Purpura, Thrombotic Thrombocytopenic[MeSH Terms]) OR (Thrombocytopenic Purpura, Thrombotic[Title/Abstract])) OR (Thrombotic Thrombocytopenic Purpura[Title/Abstract])) OR (Purpura, Thrombotic Thrombopenic[Title/Abstract])) OR (Thrombopenic Purpura, Thrombotic[Title/Abstract])) OR (Thrombotic Thrombopenic Purpura[Title/Abstract])) OR (Congenital Thrombotic Thrombocytopenic Purpura[Title/Abstract])) OR (Thrombotic Thrombocytopenic Purpura, Congenital[Title/Abstract])) OR (Familial Thrombotic Thrombocytopenic Purpura[Title/Abstract])) OR (Thrombotic Thrombocytopenic Purpura, Familial[Title/Abstract])) OR (Familial Thrombotic Thrombocytopenia Purpura[Title/Abstract]) Filters: Guideline, in the last 5 years | Guideline, in the last 5 years | (("purpura, thrombotic thrombocytopenic"[MeSH Terms] OR "thrombocytopenic purpura thrombotic"[Title/Abstract] OR "thrombotic thrombocytopenic purpura"[Title/Abstract] OR "purpura thrombotic thrombopenic"[Title/Abstract] OR ("Thrombopenic"[All Fields] AND "purpura thrombotic"[Title/Abstract]) OR "thrombotic thrombopenic purpura"[Title/Abstract] OR "congenital thrombotic thrombocytopenic purpura"[Title/Abstract] OR (((("thrombosis"[MeSH Terms] OR "thrombosis"[All Fields] OR "Thrombotic"[All Fields] OR "thrombotically"[All Fields] OR "thrombotics"[All Fields]) AND "Thrombocytopenic"[All Fields]) AND "purpura congenital"[Title/Abstract]) OR "familial thrombotic thrombocytopenic purpura"[Title/Abstract] OR (("purpura, thrombotic thrombocytopenic"[MeSH Terms] OR ("Purpura"[All Fields] AND "Thrombotic"[All Fields] AND "Thrombocytopenic"[All Fields]) OR "thrombotic thrombocytopenic purpura"[All Fields] OR ("Thrombotic"[All Fields] AND "Thrombocytopenic"[All Fields] AND "Purpura"[All Fields])) AND "Familial"[Title/Abstract]) OR "familial thrombotic thrombocytopenia purpura"[Title/Abstract]) AND | 0 |

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| | | (("filter"[All Fields] OR "filter s"[All Fields] OR "filtered"[All Fields] OR "filtering"[All Fields] OR "filterings"[All Fields] OR "filters"[All Fields]) AND ("guideline"[Publication Type] OR "guidelines as topic"[MeSH Terms] OR "guideline"[All Fields]) AND "last"[All Fields] AND "5"[All Fields] AND "years"[All Fields])) AND ((y_5[Filter]) AND (guideline[Filter])) | |
| ((((((((((((((((((Purpura, Thrombotic Thrombocytopenic[MeSH Terms]) OR (Thrombocytopenic Purpura, Thrombotic[Title/Abstract])) OR (Thrombotic Thrombocytopenic Purpura[Title/Abstract])) OR (Purpura, Thrombotic Thrombopenic[Title/Abstract])) OR (Thrombopenic Purpura, Thrombotic[Title/Abstract])) OR (Thrombotic Thrombopenic Purpura[Title/Abstract])) OR (Moschcowitz Disease[Title/Abstract])) OR (Moschkowitz Disease[Title/Abstract])) OR (Congenital Thrombotic Thrombocytopenic Purpura[Title/Abstract])) OR (Schulman-Upshaw Syndrome[Title/Abstract])) OR (Schulman Upshaw Syndrome[Title/Abstract])) OR (Upshaw-Schulman Syndrome[Title/Abstract])) OR (Upshaw Schulman Syndrome[Title/Abstract])) OR (Thrombotic Thrombocytopenic Purpura, Congenital[Title/Abstract])) OR (Upshaw Factor, Deficiency of[Title/Abstract])) OR (Microangiopathic Hemolytic | Guideline, in the last 5 years | ("purpura, thrombotic thrombocytopenic"[MeSH Terms] OR "thrombocytopenic purpura thrombotic"[Title/Abstract] OR "thrombotic thrombocytopenic purpura"[Title/Abstract] OR "purpura thrombotic thrombopenic"[Title/Abstract] OR ("Thrombopenic"[All Fields] AND "purpura thrombotic"[Title/Abstract]) OR "thrombotic thrombopenic purpura"[Title/Abstract] OR "moschcowitz disease"[Title/Abstract] OR "moschkowitz disease"[Title/Abstract] OR "congenital thrombotic thrombocytopenic purpura"[Title/Abstract] OR ("Syndrome"[Title/Abstract]) OR (("Schulman"[All Fields] AND "Upshaw"[All Fields]) AND "Syndrome"[Title/Abstract]) OR "upshaw schulman syndrome"[Title/Abstract] OR "upshaw schulman syndrome"[Title/Abstract] OR ((("thrombosis"[MeSH Terms] OR "thrombosis"[All Fields] OR "Thrombotic"[All Fields] OR "thrombotically"[All Fields] OR "thrombotics"[All Fields]) AND "Thrombocytopenic"[All Fields]) | 447 |

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| Anemia, Congenital[Title/Abstract])) OR (Thrombotic Microangiopathy, Familial[Title/Abstract])) OR (Familial Thrombotic Microangiopathy[Title/Abstract])) OR (Microangiopathy, Familial Thrombotic[Title/Abstract])) OR (Familial Thrombotic Thrombocytopenic Purpura[Title/Abstract])) OR (Thrombotic Thrombocytopenic Purpura, Familial[Title/Abstract])) OR (Familial Thrombotic Thrombocytopenia Purpura[Title/Abstract]) | | AND "purpura congenital"[Title/Abstract]) OR (("Upshaw"[All Fields] AND ("factor"[All Fields] OR "factor s"[All Fields] OR "factors"[All Fields])) AND "deficiency of"[Title/Abstract]) OR ("Microangiopathic"[All Fields] AND "hemolytic anemia congenital"[Title/Abstract]) OR (("thrombotic microangiopathies"[MeSH Terms] OR ("Thrombotic"[All Fields] AND "microangiopathies"[All Fields]) OR "thrombotic microangiopathies"[All Fields] OR ("Thrombotic"[All Fields] AND "Microangiopathy"[All Fields]) OR "thrombotic microangiopathy"[All Fields]) AND "Familial"[Title/Abstract]) OR "familial thrombotic microangiopathy"[Title/Abstract] OR (("microangiopathies"[All Fields] OR "Microangiopathy"[All Fields]) AND "familial thrombotic"[Title/Abstract]) OR "familial thrombotic thrombocytopenic purpura"[Title/Abstract] OR (("purpura, thrombotic thrombocytopenic"[MeSH Terms] OR ("Purpura"[All Fields] AND "Thrombotic"[All Fields] AND "Thrombocytopenic"[All Fields]) OR "thrombotic thrombocytopenic purpura"[All Fields] OR ("Thrombotic"[All Fields] AND "Thrombocytopenic"[All Fields] AND "Purpura"[All Fields])) AND "Familial"[Title/Abstract]) OR "familial thrombotic thrombocytopenia purpura"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter])) | |

## Appendix C. KSA Recommended Algorithm of Treatment for TTP