Immune Thrombocytopenic Purpura

CHI Formulary Indication Review

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Abbreviations

ADR - Adverse Drug Reaction

AMS – Aseptic Meningitis Syndrome

ASH - American Society of Hematology

ATRA - All-Trans Retinoic Acid

BMD - Bone Mineral Density

BTK - Bruton's Tyrosine Kinase

CADTH - Canadian Agency for Drugs and Technologies in Health

CBC - Complete Blood Count

CHI - Council of Health Insurance

CHO - Chinese Hamster Ovary

CNS - Central Nervous System

CR - Complete Response

ERR - Expected Response Rate

FcRn - AntiNeonatal Fc receptor

GEPTI - Spanish Immune Thrombocytopenia Group

GI - Gastrointestinal

HAMA/HACA Titer - Human Anti-Mouse Antibody/Human Anti-Chimeric Antibody Titer

HAS - Haute Autorité de Santé

HBV - Hepatitis B Virus

HRQoL - Health-Related Quality of Life

HTA - Health Technology Assessment

i.v. - Intravenous

IDF - Insurance Drug Formulary

IgG - Immunoglobulin G

INR - International Normalized Ratio

IQWIG - Institute for Quality and Efficiency in Health Care (Germany)

ISMP - Institute for Safe Medication Practices

ITP - Immune Thrombocytopenia

IV - Intravenous

IVC - Inferior Vena Cava

IVIG - Intravenous Immunoglobulin

KSA - Kingdom of Saudi Arabia

LWMH - Low Molecular Weight Heparin

N/A - Not Applicable

NHL - Non-Hodgkin Lymphoma

NICE - National Institute for Health and Care Excellence (UK)

PBAC - Pharmaceutical Benefits Advisory Committee

PBS - Pharmaceutical Benefits Scheme

PML - Progressive Multifocal Leukoencephalopathy

PR – Partial Response

PUVA - Psoralens plus Ultraviolet A

QoL - Quality of Life

REMS - Risk Evaluation and Mitigation Strategy

Rh (D) - Rhesus factor (D)

Rho+ - Rhesus positive

s.c. - Subcutaneous

SARS-COV-2 - Severe Acute Respiratory Syndrome Coronavirus 2

SFDA - Saudi Food and Drug Authority

SRR - Sustained Response Rate

SYK - Spleen Tyrosine Kinase

TIA - Transient Ischemic Attack

TPO-RA - Thrombopoietin Receptor Agonist

US - United States

UVB - Ultraviolet B

VHBC - Viral Hepatitis B and C

VTE – Venous Thromboembolism

Executive Summary

Immune thrombocytopenia (ITP) is an immune-mediated acquired disease in adults or children characterized by a transient or persistent decrease of the platelet count and an increased risk of bleeding with time. In some cases, ITP resolves, either on its own or with treatment. In other cases, ITP develops into a chronic condition, which means symptoms can be treated, but not cured. People with chronic ITP may need lifelong treatment.[1]

ITP is also known as autoimmune thrombocytopenic purpura, immune thrombocytopenic purpura, idiopathic thrombocytopenic purpura, Werlhof disease, and autoimmune thrombocytopenia. This condition can be classified as **primary** (autoimmune disorder) or **secondary** ITP (due to underlying conditions such as chronic infections or hematological cancers). It can also be categorized into 3 phases: **acute** ITP (symptoms resolve within 3 months, mainly in children), **persistent** ITP (symptoms resolve within 3-12 months), and **chronic** ITP (disease lasts for a year or more).[1] An additional phase is termed refractory ITP, which consists of cases that fail to resolve with splenectomy.[2]

The acute form presents in childhood, affects both sexes, and may be preceded by a viral infection. 85% of children have a benign course: they do not require treatment and usually recover within 3 months. Chronic ITP affects individuals aged between 20 and 50 years, with a female/male ratio of 3 to 1.[3]

Patients with ITP might suffer from petechiae, purpura, bruises, bleeding gums, blood in urine or stools, nosebleeds, heavy menstrual periods, and fatigue.[1] Complications include heaving bleeding during delivery for women, and rarely brain hemorrhage.[4]

This disease is considered rare, with approximately 4 in 100,000 children and 3 in 100,000 adults found to have ITP each year in the United States (US).[1] Among patients requiring formal medical care, the economic burden during the first 12 months following diagnosis is high, with estimated US expenditures totaling over $400 million.[5] Saudi epidemiologic and outcome data about ITP are scarce.[6]

The mainstay treatment of ITP includes corticosteroids to temporarily block the antibodies that destroy platelets, intravenous immunoglobulin (IVIG) or thrombopoietin receptor agonists (TPO-RAs) to boost platelet production, or immunosuppressants to suppress the immune system. Splenectomy can be an option in severe cases.[1]

This report compiles all clinical and economic evidence related to ITP according to the relevant sources. The ultimate objective of issuing ITP 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 ITP 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 ITP 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 ITP.

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medications in ITP 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 recommendations based on the different ITP guidelines used to issue this report:

Table 1. General Recommendations for the Management of Immune Thrombocytopenia (ITP)

Management of Immune Thrombocytopenia		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
The first-line treatment is similar in most cases of primary and secondary ITP, namely, glucocorticoids and/or IVIg. when choosing the second-line option, one must consider seriously the underlying disease when managing secondary ITP.	Not graded	GEPTI 2023[7]
The choice of treatment should be individualized, involving a discussion with the patient, consideration of the severity of the bleeding episodes, comorbidities, the toxicity profile of each therapy option, drug availability,	Not graded	Expert Saudi Panel 2019[6]

anticipated surgical procedures, the cost of therapy, and patient age, lifestyle, and quality of life.		
Most patients with no or minimal bleeding (limited to skin manifestations only) may be observed, provided that their platelet count continues to be >20–30 × 10^9 /L	Grade 2C (Consensus guideline sin Australia and New Zealand 2022)	Expert Saudi Panel 2019[6], Consensus guidelines in Australia and New Zealand 2022[8]
Inpatient management is suggested for patients with newly diagnosed ITP who have a platelet count below 20 × 10^9/L and are asymptomatic or have minor symptoms.	Conditional recommendation, very low certainty of evidence	ASH 2019 Guidelines [9]
For patients with a platelet count at the lower end of this threshold, those with additional comorbidities, anticoagulant or antiplatelet agents, or need to follow the procedures. Corticosteroid treatment may be appropriate for elderly patients (aged > 60 years).	Not graded	Korean 2022 experts recommendations[10]
First-line medications include corticosteroids, intravenous immunoglobulin (IvIg), or anti-D immunoglobulin (anti-D). o IVIG is useful in the emergency settings (ongoing bleeding, surgery) o Use of Anti-D is limited to Rh +ve patients who have an acceptable hemoglobin level and a functional spleen.	Not graded	Expert Saudi Panel 2019[6]
o Patients who fail to exhibit significant response with first-line therapy or relapse after the initial response, require second-line therapy. o Not all second-line options are similar. Therefore, factors including comorbidities, age, and patient	Not graded	Expert Saudi Panel 2019[6]

preference play a major role in the choice of therapy. o Options include rituximab, thrombopoietin receptor agonists (TPO-RAs), mycophenolate mofetil, danazol, dapsone, azathioprine, cyclosporine A, cyclophosphamide, and vinca alkaloids.		
In patients who fail second-line therapies or in cases of bleeding emergency that is life-threatening, splenectomy will continue to be an important option.	Not graded	Expert Saudi Panel 2019[6]
- Combined therapies are usually more effective than monotherapy in refractory patients. Ideally, agents with different mechanisms of action should be combined. Rescues have been described using steroids concomitantly with rituximab or TPO-RA. - In the event of no response to one treatment, adding a new therapy concomitantly may be better than suspending the former and starting with the new one only.	Not graded	GEPTI 2023[7]
Fostamatinib was approved for the treatment of chronic ITP in adults in 2018.	Not graded	Expert Saudi Panel 2019[6]
Duration of therapy: Recommends in favor of short course (≤ 6 weeks) and against longer course of prednisone (> 6 weeks including taper). Treatment should not last more than three cycles in the case of dexamethasone.	Strong recommendation, very low certainty of evidence[9]	ASH 2019 Guidelines[9], GEPTI 2023[7], Korean 2022 experts recommendations[10]
In life-threatening bleeding, the guidelines recommend platelet transfusions to achieve hemostasis, along with IVIg (1–2 g/kg), and steroids (methylprednisolone up to 1000 mg	Grade 1D	Consensus guideline sin Australia and New Zealand 2022[8]

intravenous daily for 1–5 days or high dose dexamethasone 40 mg daily intravenous or orally for 4 days)		
Vinka alkaloids can be considered for rare cases of refractory or multiply relapsed disease and life-threatening bleeding	Grade 2D	Consensus guideline sin Australia and New Zealand 2022[8]
In pediatric patients: o First line options include prednisone, methylprednisolone, and high dose IVIG. o Second options in persistent ITP include IV Anti-D Ig (if Rh+) + steroids combination. o In chronic ITP, TPO-RA long term is recommended. o Third line options include Mycophenolate mofetil, Rituximab, and dapsone.	Not graded	GEPTI 2023[7]
In elderly patients: o When there is severe bleeding, hospitalization and immediate instauration of treatment is recommended. o First-line options – in the presence of severe bleeding or without: IVIG with corticosteroids combination. o Additional options when rapid increases in platelet counts are required: TPO-RA and Vinca alkaloids	Not graded	GEPTI 2023[7]
In pregnant patients: o First line options include prednisone or IVIG when prednisone-induced side effects, severe bleeding, or requirement of rapid recovery of platelets to prepare for delivery.	Not graded	GEPTI 2023[7]

○ Other options include Azathioprine, cyclosporin. If splenectomy is decided (data regarding safety/efficacy are limited, risk of neonatal Thrombocytopenia), the procedure should be performed in the second trimester. ○ Management of neonates will depend on their platelet count values		

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

Table 2. Summary of SFDA-Registered Drug Therapies for the ITP

Medication	Indication	Line of Therapy	Level of Evidence/ Recommendation	HTA Recommendations
Prednisone, methylprednisolone, and dexamethasone	In all confirmed ITP cases	**1st**	Not graded [6–8,10,11]	N/A
IVIG	IVIG is useful in the emergency settings (ongoing bleeding, surgery)	**1st**	Not graded [6–8,10,11]	N/A
Anti-D (Rho+) Immunoglobulin	Use of Anti-D is limited to Rh +ve patients who have an acceptable hemoglobin level and a functional spleen.	**1st**	Not graded [6–8,10,11]	N/A
Mycophenolate mofetil	In patients who fail to respond to first-line therapy or relapse after the initial response	**2nd**	Not graded [6–8,10,11]	N/A
Rituximab	In patients who fail to respond to first-line	**2nd**	Not graded [6–8,10,11]	N/A

	therapy or relapse after the initial response			
Cyclosporine	In patients who fail to respond to first-line therapy or relapse after the initial response	**2nd**	Not graded [6–8,10,11]	N/A
Cyclophosphamide	In patients who fail to respond to first-line therapy or relapse after the initial response	**2nd**	Not graded [6–8,10,11]	N/A
Vincristine	In patients who fail to respond to first-line therapy or relapse after the initial response	**2nd**	Not graded [6–8,10,11]	Moderate recommendation in ITP resistant to usual treatments from HAS[12]
Vinblastine	In patients who fail to respond to first-line therapy or relapse after the initial response	**2nd**	Not graded [6–8,10,11]	N/A
Azathioprine	In patients who fail to respond to first-line therapy or relapse after the initial response	**2nd**	Not graded [6–8,10,11]	Positive recommendation from HAS[13]

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 Recommendations

1.1.1 Management of Adult Immune Thrombocytopenia: Recommendations by an Expert Saudi Panel (2019)

This **review article** published by Al-Zahrani et al. in the Journal of Applied Hematology in 2019 focuses on the expert opinion based on local experience in the field, in light of relevant literature and guidelines, and provides expert recommendations for the diagnosis and management of adult patients with ITP in Saudi Arabia.[6]

The main recommendations are summarized below.

- The choice of treatment should be individualized, involving a discussion with the patient, consideration of the severity of the bleeding episodes, comorbidities, the toxicity profile of each therapy option, drug availability, anticipated surgical procedures, the cost of therapy, and patient age, lifestyle, and quality of life.
- All patients should be counseled regarding lifestyle changes and medications to avoid, including aspirin and other nonsteroidal anti-inflammatory drugs.
- Most patients with no or minimal bleeding (limited to skin manifestations only) may be observed, provided that their platelet count continues to be > 20–30 x 10^9/L.

First line management

First-line medications include corticosteroids, intravenous immunoglobulin (IvIg), or anti-D immunoglobulin (anti-D).

Corticosteroids:

- Standard first-line therapy and expected to induce a clinically meaningful response in 3–5 days but may take longer.
- Caution is required while using steroids for the following patient populations:
    - Patients with type 2 diabetes
    - Those with uncontrolled hypertension
    - Pregnant women
    - Elderly individuals

    - Those with an active viral illness
- Corticosteroids may be used in the following manner:
    - Dexamethasone 40 mg/day for 4 days (can be repeated monthly up to four cycles).
    - Prednisolone 0.5–2 mg/kg/day for 2–4 weeks, and taper once response is observed.
    - Pulse methylprednisolone.

Intravenous immunoglobulin (IvIg):

- Can induce a rapid response within 1–2 days and is therefore useful in emergency settings (ongoing bleeding, surgery).
- IvIg is expensive and is not without side effects which include anaphylaxis, renal failure, and thrombosis.
- IvIg is usually given at a dose of 1 g/kg/day for 1–2 days.

Anti-D immunoglobulin:

- Not commonly used; should be used with caution given some recent reports of severe and fatal hemolysis.
- Not advised in patients with active bleeding causing a decline in hemoglobin or those with evidence of autoimmune hemolysis.
- Use of Anti-D is limited to Rh +ve patients who have an acceptable hemoglobin level and a functional spleen.

Second line management

- Patients who fail to exhibit significant response with first-line therapy or relapse after the initial response, require second-line therapy. About 20% of patients fail first-line therapy including splenectomy, and an estimated 10%–20% experience eventual relapse after splenectomy.
- Due to improved awareness on therapeutic options for ITP, many patients are hesitant to undergo splenectomy and prefer to try other medical therapies first.
- Not all second-line options are similar. Therefore, factors including comorbidities, age, and patient preference play a major role in the choice of therapy.
- The table below showcases the therapeutic agents and their doses for immune thrombocytopenia patients who fail to respond to first-line therapy or relapse after the initial response.

Table 3. The Therapeutic Agents and their Doses for Immune Thrombocytopenia Patients Who Fail to Respond to First-Line Therapy or Relapse after the Initial Response

Therapeutic agent	Dose
Rituximab	375 mg/m2 weekly for 4 doses
TPO-RA (Thrombopoietin receptor agonists)	Eltrombopag: 25-75 mg orally daily, continuous therapy Romiplostim: 1-10 mcg/kg subcutaneously once a week, continuous therapy
Danazol	100-800 mg orally daily in divided doses
Dapsone	75-100 mg orally daily
Azathioprine	2 mg/kg oral daily
Cyclosporine A	2.5-5 mg/kg of body weight per day (dose to be adjusted by blood level, target 100-400 ng/ml)
Mycophenolate mofetil	1-2 g/day
Cyclophosphamide	300-1000 mg/m2, 2-4 weekly for up to 4 doses; maintenance dose 1-2 mg/kg daily
Vinca alkaloids	Vincristine: 1-2 mg weekly for up to 3-4 doses Vinblastine: 6 mg/m2 (maximum 10 mg total dose/injection), weekly for 3-4 doses

Splenectomy as a second line therapy:

- Although a safe procedure, many physicians are also hesitant to refer patients because of the potential risk of surgical and other complications, such as increased risk of infection and thrombosis and possible requirement for additional intervention(s).
- In patients who fail second-line therapies such as rituximab and TPO-RA, splenectomy will continue to be an important option.
- ITP patients should receive appropriate postoperative thromboprophylaxis as well as prophylactic polyvalent pneumococcal, meningococcal C conjugate, and Haemophilus influenza B vaccines at least 4 weeks before (preferably) or

2 weeks after splenectomy. In addition, patients should be revaccinated every 5 years after splenectomy and receive antibiotic (penicillin) prophylaxis.

Newer agents or ITP

Fostamatinib:

- Fostamatinib is a spleen tyrosine kinase (SYK) inhibitor that is orally bioavailable.
- It was approved for the treatment of chronic ITP in adults in 2018.
- Its approval was based on favorable results in 2 phase III clinical trials in adults with persistent or chronic ITP after failure of other therapies including rituximab, TPO-RA, and/or splenectomy.
- The median time to response was 15 days.
- Most common adverse effects include gastrointestinal toxicity and hypertension.

Avatrombopag:

- This is another TPO-RA and was approved in May 2019 for the treatment of adult patients with chronic ITP who have had an insufficient response to a previous treatment.

Rozanolixizumab:

- Rozanolixizumab is an antineonatal Fc receptor (FcRn) inhibitor that decreases circulating pathologic IgG by blocking FcRn.
- Studies in murine autoimmune disease demonstrated favorable results, so the effect of this agent was evaluated in ITP and other autoimmune diseases. The interim analysis of an ongoing phase II multiple dose study of rozanolixizumab in adult ITP showed encouraging results with 30 percent of treated patients achieving an improvement in the platelet count.

Monoclonal antibodies and other thrombopoietin agonists with the potential to enhance platelet production are in various stages of development and hold promise for the future.

1.2 North American Guidelines

1.2.1 American Society of Hematology (ASH) Guidelines for Immune Thrombocytopenia (2019)

These evidence-based guidelines of the American Society of Hematology (ASH) are intended to support patients, clinicians, and other health care professionals in their decisions about the management of ITP.[9]

In 2015, ASH formed a multidisciplinary guideline panel that included 8 adult clinical experts, 5 pediatric clinical experts, 2 methodologists with expertise in ITP, and 2 patient representatives. The panel was balanced to minimize potential bias from conflicts of interest. The panel reviewed the ASH 2011 guideline recommendations and prioritized questions. The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, including evidence-to-decision frameworks, to appraise evidence (up to May 2017) and formulate recommendations.

There was a lack of evidence to support strong recommendations for various management approaches. In general, strategies that avoided medication side effects were favored.

Management of adult patients with newly diagnosed ITP

<u>Corticosteroids versus observation</u>

- In adults with newly diagnosed ITP and a platelet count of < 30 x 10^9 /L who are asymptomatic or have minor mucocutaneous bleeding, the panel suggests corticosteroids rather than management with observation (conditional recommendation based on very low certainty in the evidence of effects).
- In adults with newly diagnosed ITP and a platelet count of ≥ 30 x 10^9 /L who are asymptomatic or have minor mucocutaneous bleeding, the panel recommends against corticosteroids and in favor of management with observation (strong recommendation based on very low certainty in the evidence of effects).
- The treating physician should ensure that the patient is adequately monitored for potential corticosteroid side effects regardless of the duration or type of corticosteroid selected. This includes close monitoring for hypertension, hyperglycemia, sleep and mood disturbances, gastric irritation or ulcer formation, glaucoma, myopathy, and osteoporosis. Given the potential impact of corticosteroids on mental health, the treating physician should assess

health-related quality of life (HRQoL) (depression, fatigue, mental status, etc) while patients are receiving corticosteroids (good practice statement).

Inpatient versus outpatient management

- In adults with newly diagnosed ITP and a platelet count of < 20 x 10^9 /L who are asymptomatic or have minor mucocutaneous bleeding, the ASH guideline panel suggests admission to the hospital rather than management as an outpatient (conditional recommendation based on very low certainty in the evidence of effects).
- In adults with an established diagnosis of ITP and a platelet count of < 20 x 10^9 /L who are asymptomatic or have minor mucocutaneous bleeding, the panel suggests outpatient management rather than hospital admission (conditional recommendation based on very low certainty in the evidence).
- In adults with a platelet count of ≥ 20 x 10^9 /L who are asymptomatic or have minor mucocutaneous bleeding, the panel suggests management as an outpatient rather than hospital admission (conditional recommendation based on very low certainty in the evidence of effects).
- The referring physician should ensure that the patient has follow-up with a hematologist within 24 to 72 hours of the diagnosis or disease relapse (good practice statement).

Duration and type of corticosteroids

- In adults with newly diagnosed ITP, the panel recommends against a prolonged course (> 6 weeks including treatment and taper) of prednisone and in favor of a short course (≤ 6 weeks) (strong recommendation based on very low certainty in the evidence of effects).
- In adults with newly diagnosed ITP, the panel suggests either prednisone (0.5-2.0 mg/kg per day) or dexamethasone (40 mg per day for 4 days) as the type of corticosteroid for initial therapy (conditional recommendation based on very low certainty in the evidence of effects).

Rituximab as initial treatment

- In adults with newly diagnosed ITP, the panel suggests corticosteroids alone rather than rituximab and corticosteroids for initial therapy (conditional recommendation based on very low certainty in the evidence of effects).

Management of adults with ITP who are corticosteroid-dependent or do not have a response to corticosteroids

Eltrombopag versus romiplostim

- In adults with ITP for ≥ 3 months who are corticosteroid-dependent or unresponsive to corticosteroids and are going to be treated with a thrombopoietin receptor agonist (TPO-RA), the panel suggests either eltrombopag or romiplostim (conditional recommendation based on very low certainty in the evidence of effects).

Second-line therapies

- In adults with ITP lasting ≥ 3 months who are corticosteroid-dependent or have no response to corticosteroids, the panel suggests either splenectomy or a TPO-RA (conditional recommendation based on very low certainty in the evidence of effects).
- In adults with ITP lasting ≥ 3 months who are corticosteroid-dependent or have no response to corticosteroids, the panel suggests rituximab rather than splenectomy (conditional recommendation based on very low certainty in the evidence of effects).
- In adults with ITP lasting ≥ 3 months who are corticosteroid-dependent or have no response to corticosteroids, the panel suggests a TPO-RA rather than rituximab (conditional recommendation based on very low certainty in the evidence of effects).
- The treating physician should ensure that patients have appropriate immunizations prior to splenectomy and that they receive counseling regarding antibiotic prophylaxis following splenectomy. The treating physician should also educate the patient on prompt recognition and management of fever and refer to current recommendations on pre- and post-splenectomy care (good practice statement).

Management of children with newly diagnosed ITP

Outpatient versus inpatient management

- In children with newly diagnosed ITP and a platelet count of < 20 x 10^9 /L who have no or mild bleeding (skin manifestations) only, the panel suggests against admission to the hospital and in favor of management as an outpatient (conditional recommendation based on very low certainty in the evidence of effects).
- In children with newly diagnosed ITP and a platelet count of ≥ 20 x 10^9 /L who have no or mild bleeding (skin manifestations) only, the panel suggests against admission to the hospital and in favor of management as an

outpatient (conditional recommendation based on very low certainty in the evidence of effects).

- The referring physician should ensure that the patient has follow-up with a hematologist within 24 to 72 hours of diagnosis (good practice statement).

Treatment versus observation

- In children with newly diagnosed ITP who have no or minor bleeding, the panel suggests observation rather than corticosteroids (conditional recommendation based on very low certainty in the evidence of effects).
- In children with newly diagnosed ITP who have no or minor bleeding, the panel recommends observation rather than IV immunoglobulin (IVIG) (strong recommendation based on moderate certainty in the evidence of effects).
- In children with newly diagnosed ITP who have no or minor bleeding, the panel recommends observation rather than anti-D immunoglobulin (strong recommendation based on moderate certainty in the evidence of effects).

Corticosteroid duration and type

- In children with newly diagnosed ITP who have non–life threatening mucosal bleeding and/or diminished HRQoL, the panel recommends against courses of corticosteroids longer than 7 days and in favor of courses 7 days or shorter (strong recommendation based on very low certainty in the evidence of effects).
- In children with newly diagnosed ITP who have non–life-threatening mucosal bleeding and/or diminished HRQoL, the panel suggests prednisone (2-4 mg/kg per day; maximum, 120 mg daily, for 5-7 days) rather than dexamethasone (0.6 mg/kg per day; maximum, 40 mg per day for 4 days) (conditional recommendation based on very low certainty in the evidence of effects).

Treatment of children with non-life-threatening bleeding and/or diminished HRQoL

- In children with newly diagnosed ITP who have non–life-threatening mucosal bleeding and/or diminished HRQoL, the panel suggests corticosteroids rather than anti-D immunoglobulin (conditional recommendation based on low certainty in the evidence of effects).
- In children with newly diagnosed ITP who have non–life-threatening mucosal bleeding and/or diminished HRQoL, the panel suggests either anti-D immunoglobulin or IVIG (conditional recommendation based on low certainty in the evidence of effects).
- In children with newly diagnosed ITP who have non–life-threatening mucosal bleeding and/or diminished HRQoL, the panel suggests corticosteroids rather

than IVIG (conditional recommendation based on low certainty in the evidence of effects).

Management of children with ITP who do not have a response to first-line treatment

Second-line therapies: splenectomy, TPO-RA, and rituximab compared one against the other

- In children with ITP who have non–life-threatening mucosal bleeding and/ or diminished HRQoL and do not respond to first-line treatment, the panel suggests the use of TPO-RAs rather than rituximab (conditional recommendation based on very low certainty in the evidence of effects).
- In children with ITP who have non–life-threatening mucosal bleeding and/or diminished HRQoL and do not respond to first-line treatment, the panel suggests TPO-RAs rather than splenectomy (conditional recommendation based on very low certainty in the evidence of effects).
- In children with ITP who have non–life-threatening mucosal bleeding and/or diminished HRQoL and do not respond to first-line treatment, the suggests rituximab rather than splenectomy (conditional recommendation based on very low certainty in the evidence of effects).
- The treating physician should ensure that the patient has appropriate immunizations prior to splenectomy and that they receive counseling regarding antibiotic prophylaxis following splenectomy. The treating physician should educate the patient on prompt recognition and management of fever and refer to current recommendations on pre- and post-splenectomy care (good practice statement).

1.3 European Guidelines

1.3.1 Spanish ITP Working Group (GEPTI) Recommendations for the Clinical Approach to Immune Thrombocytopenia (2023)

The aim behind this consensus document is to provide a practical tool to facilitate the integral management of all aspects of primary ITP management[7].

Consensual definitions and concepts in the context of ITP were included:

- Primary ITP Categories According to the Phase of the Disease:
    - Newly diagnosed ITP: within 3 months from diagnosis.
    - Persistent ITP: between 3 and 12 months from diagnosis.
    - Chronic ITP: lasting for more than 12 months from diagnosis.

    - Severe ITP: there are bleeding symptoms sufficient to mandate treatment, or new bleeding symptoms requiring additional therapeutic intervention with either an increased dose or a different platelet-enhancing agent.

- Refractory ITP - Two criteria must be met:
    - Failure of splenectomy or subsequent relapse.
    - Severe ITP or bleeding risk that in the opinion of the attending physician requires therapy.
- Type of response
    - Complete response: platelet count ≥ 100 x 10^9/L and absence of bleeding.
    - Response: platelet count ≥ 30 x 10^9/L and at least doubling of the baseline count, and absence of bleeding.
    - No response: platelet count < 30 x 10^9/L or less than doubling of the baseline count, or bleeding.
    - Corticosteroid dependence: the ongoing need for corticosteroid administration for at least for 2 months to maintain a platelet count ≥ 30 x 10^9/L and/or to avoid bleeding.
- Type of response
    - Durable response: platelet count ≥ 30 x 10^9/L and at least doubling baseline at 6 months.
    - Early response: platelet count ≥ 30 x 10^9/L and at least doubling baseline at 1 week.
    - Initial response: platelet count ≥ 30 x 10^9/L and at least doubling baseline at 1 month.
    - Maintained response in the absence of treatment: response after 6 months without treatment.

<u>First line treatment of primary ITP</u>:

- Decision relies basically on bleeding symptoms and platelet counts (<20 x 10^9/L).
- First-line treatment is **glucocorticoids** (prednisone 0.5–1 mg/kg or dexamethasone 40 mg/day for 4 days).
- Treatment should not last more than 8 weeks in the case of prednisone or more than three cycles in the case of dexamethasone. ERR prednisone: 60–80%; SRR prednisone: 30–50%.

- Potential side effects of glucocorticoids other than those linked to immunosuppression are ecchymosis, skin thinning and atrophy, acne, mild hirsutism, facial erythema, stria, impaired wound healing, thinning of hair, perioral dermatitis, and adverse gastrointestinal effects.
- **IVIg** is reserved for patients with severe hemorrhage or when steroids are contraindicated. ERR IVIg: 75–92%; SRR IVIg: 30–55%.
- In severe hemorrhage scenarios, **combined treatment** is suitable (IVIg, high-dose methylprednisolone, platelet transfusion; consider whether antifibrinolytics and/or TPO-RA are required).
- Potential side effects of IVIg are chills, fever, flushing, flu-like muscle pains or joint pains, nausea, fatigue, rash, vomiting and very rarely, allergic reactions or anemia.
- **Anti-D immunoglobulins** may be used, although they are not available world-wide. The single i.v. dose is 50–75 g/kg, ERR is 80–90% and SRR at 60 days is 17%. A potential side effect is secondary hemolytic anemia in Rh(D) positive patients.
- Hospitalization for at least 48–72 h is recommended for newly diagnosed patients with platelet counts < 20 x 10^9/L.

Antimicrobial prophylaxis:

- Prophylaxis with trimethoprim–sulfamethoxazole at 80 mg/400 mg twice a day two to three times a week to prevent infection by Pneumocystis carinii must be administered in the following cases:
    - Patients on steroid treatment lasting >4 weeks at daily doses >30 mg;
    - Patients on prednisone > 8 weeks at 15–30/mg/day; patients combining 15–30/mg/day prednisone with cyclosporine;
    - Patients with prednisone at >10mg/day and meeting ≥ two of the following criteria: age >65 years, pulmonary disease, and concomitant use of another immunosuppressant.
- Prophylaxis against herpes virus with acyclovir at 400 mg/day is advisable for patients >60 years old, patients on prednisone at daily doses >7.5 mg or patients with a history of infection with this pathogen.
- Prophylaxis with entecavir at 0.5 mg/day is recommended for those patients with antibodies against viral hepatitis B and C (VHBC) and a positive test for hepatitis B virus (HBV) antigen, who are on treatment with prednisone either at >10 mg/day during ≥8 weeks, or at >20 mg/day during >4 weeks. If the test for antibodies against VHBC was positive but that for HBV antigen was negative, the patient should be periodically monitored.

- Prophylaxis to prevent osteoporosis with calcium and vitamin D (colecalciferol at a weekly dose of 2800 IU) is recommended for postmenopausal women, >50 years old (y.o.) male patients who have been on steroid treatment for >3 months, and in those patients who have a T-score of bone mineral density (BMD) < -1.5 and are being treated or are to be treated with steroids at doses >2.5 mg/day for >3 months. This prophylaxis should be applied to premenopausal women and <50 y.o. male patients only in the event of a history of previous fractures or when the T-score is <-1.5 and treatment with steroids at doses >5 mg/day for >3 months is being administered or planned.

Second-line treatment of primary ITP:

- The first choice should be **TPO-RA** (eltrombopag, romiplostim, avatrombopag) or fostamatinib.
- TPO-RA exhibits a good safety profile, although its cost is high. The choice of one TPO-RA or another should be based on administration route, patient preference and potential future complications.
- ERR eltrombopag: 70–80%; SRR eltrombopag: 10–30%; ERR romiplostim: 70–80%; SRR romiplostim: 10–30%; ERR avatrombopag: 65%; SRR avatrombopag: not known.
- TPO-RA may increase the risk of venous thromboembolism. Other potential side effects are headache, tiredness, arthralgias, nausea and nasopharyngitis.
- **Fostamatinib** is a SYK inhibitor able to reduce the anti-platelet activity of phagocytes ERR fostamatinib: 18–43%.
- Responses to fostamatinib are observed early, and good results in multirefractory patients have been described.
- Fostamatinib is particularly suitable as a first option for second-line treatment in patients with high thromboembolic risk.
- Potential side effects of fostamatinib are blood pressure increase, liver toxicity, severe diarrhea, and infections.
- **Rituximab** should be the secondary scenario in second-line options. The more used regimen consists of four doses of 375 mg/m2 each, administered on a weekly basis. Nevertheless, the same temporal pattern reducing each dose from 375 to 100 mg/m2 has been shown to have the same efficacy, while being possibly safer.
- ERR rituximab: 60–80%; SRR rituximab: 20–30%.
- Potential side effects of rituximab other than those linked to immunosuppression are infusion-related reactions (special attention has to be

paid to fever, chills, shaking, dizziness, trouble breathing, itching or rash, lightheadedness or fainting), body aches, tiredness and nausea.

- **Splenectomy** can be considered in chronic phases after at least one second-line treatment has failed.
- ERR splenectomy: 80–90%; SRR splenectomy: 60–70%.
- The laparoscopic procedure is preferred if splenectomy is finally decided.
- Potential side effects of splenectomy other than infection risk are pancreatitis/fistula, atelectasis, bleeding, or pulmonary embolism.

Management of refractory patients with ITP:

- There is no clear recommendation about how those refractory patient treatments should be managed.
- Combined therapies are usually more effective than monotherapy in refractory patients. Ideally, agents with different mechanisms of action should be combined. Rescues have been described using steroids concomitantly with rituximab or TPO-RA.
- In the event of no response to one treatment, adding a new therapy concomitantly may be better than suspending the former and starting with the new one only.
- Other diagnoses, such as drug-induced thrombocytopenia, myelodysplastic syndrome, or hereditary thrombocytopenia, should be considered in multi-refractory patients.
- The use of immunosuppressants, immunomodulators or cytostatic agents can be considered. Nevertheless, their side effects, especially those linked to an increased infection risk, make it advisable to carefully balance the benefit to risk ratio.

The table below details the management of emergency and scheduled surgeries:

Table 4. GEPTI 2023 Recommendations for the Management of Emergency and Scheduled Surgeries

Time to surgery	Therapeutic options (one or more)	Remarks
< 12–24 h	Dexamethasone, 40 mg/day x 4 days IVIg, 1 g/kg/day x 2 days Peri/intra-surgical platelet transfusion	Contact blood bank to arrange strategy and required resources

1–7 days	Dexamethasone, 40 mg/day x 4 days IVIg, 1 g/kg/day x 2 days	Platelet transfusion is a valid option for those cases where no response to previous measures is observed
< 2 weeks	Dexamethasone, 40 mg/day x 4 days IVIg, 1 g/kg/day x 2 days Eltrombopag, 50 mg/day Romiplostim, 3 microg/kg/week Avatrombopag, 20 mg/day	
4 weeks	Dexamethasone, 40 mg/day x 4 days Prednisone, 0.5–1 mg/kg/day Eltrombopag, 50 mg/day Romiplostim, 3 microg/kg/week Avatrombopag, 20 mg/day	

The GEPTI 2023 recommendations regarding the management of primary ITP in special populations such as pediatrics, elderly and pregnant women were also included:

Pediatric population:

- Therapeutic decisions should not rely on platelet counts only. The type of bleeding manifestations and hemorrhagic risk factors have also to be considered.
- The aim of the treatment should prioritize the control of clinically relevant hemorrhages.
- First-line options
    - Oral prednisone or i.v. methylprednisolone, 4 mg/kg/day (maximum dose 180 mg/day in three daily doses) for 4 days, 2 mg/kg for 3 days, then suspend.
    - High-dose IVIg, one single dose of 0.8–1 g/kg.
- Second-line options - In persistent ITP
    - (If Rh+) i.v. anti-D Ig, one dose of 50–75 g/kg, one-hour perfusion.
    - Methylprednisolone, i.v., 30 mg/kg/day for 3 days, 2 h perfusion.

    - Dexamethasone, oral, 0.6 mg/kg/day (one daily dose, 40 mg/day maximum dose) for 4 days each month.
- Second-line options - In chronic ITP is TPO-RA (long-term treatment):
    - Romiplostim, s.c., one weekly dose, initial dose 1 microg/kg, weekly increases of 1 microg (10 microg maximum dose) until platelet counts ≥ 50 x 10^9/L are reached.
    - Eltrombopag, oral daily dose of 25 mg (<6 years) or 50 mg (≥6 years). If platelet counts remain <50 x 10^9/L after 2 weeks, increase daily dose in 12.5 mg (<6 years) or 25 mg (≥6 years). This pattern is repeated until platelet counts > 50 x 10^9/L are reached, never using daily doses >75 mg.
- Third-line options
    - Mycophenolate mofetil, 20–40 mg/kg/day orally, in two daily doses (response in 4–6 weeks).
    - Rituximab, currently under surveillance for suspicion of risk of progressive multifocal leukoencephalopathy; furthermore, risk of infection due to prolonged B-cell depletion. Infusion must be closely monitored to anticipate acute immunoallergic reactions.
    - Dapsone has shown a good efficacy/safety profile in pediatric patients refractory to steroids
- Splenectomy:
    - In ITP of new or persistent diagnosis, if there is a bleeding emergency that is life-threatening and does not respond to previous treatment.
    - In chronic ITP, if there is a life-threatening bleeding emergency.
    - Can be considered in patients > 5 years of age and > 2 years evolution who are symptomatic and refractory to previous treatments, if ITP interferes the normal life development.

<u>Elderly patients</u>:

- Differential diagnosis is particularly important to reliably discard other entities and avoid wrong therapeutic approaches.
- The aim of the treatment is to maintain platelet counts ≥ 30 x 10^9/L in patients >75 y.o. (or in those >60 y.o. if there are concomitant bleeding risk factors) and improve QoL.
- When there is severe bleeding, hospitalization and immediate instauration of treatment is recommended.
- First-line options – in the presence of severe bleeding:

    - IVIg, 0.4–0.5 g/kg/day during no more than 5 days (controlling hydration and renal function). Administer concomitantly with corticosteroids.
    - Prednisone, but change to second-line in the event that doses >5 mg/day were required for >3 months to maintain the desired platelet count. Do not prolong treatment beyond 6–8 weeks.
    - Dexamethasone (avoid if possible; if chosen, avoid administering more than two to three cycles; these should not exceed 20 mg/day or 4 days).
    - Additional options when rapid increases in platelet counts are required:
        - TPO-RA: romiplostim, eltrombopag, avatrombopag.
        - Vinca alcaloids: vinblastine, vincristine.
- First-line options – in the absence of bleeding:
    - Prednisone, but change to second-line in the event that doses >5 mg/day are required for >3 months to maintain the desired platelet count. Do not prolong treatment beyond 6–8 weeks.
    - Dexamethasone (avoid if possible; if chosen, avoid administering more than two to three cycles; these should not exceed 20 mg/day or 4 days).
    - IVIg (only with severe thrombocytopenia [$<10 \times 10^9$/L] or when bleeding risk is unacceptable), 0.4–0.5 g/kg/day for no more than 5 days, controlling hydration and renal function, and being administered concomitantly with corticosteroids.
- Second-line options – in the absence of bleeding:
    - TPO-RA (first choice, ahead of the other second-line drugs).
    - Eltrombopag, oral daily dose of 25–75 mg.
    - Romiplostim, s.c., weekly dose of 1 microg/kg; if needed, increase dose progressively, never exceeding 10 microg/kg, until the target platelet count is reached. We suggest starting with 3 microg/kg/week to optimize time to response.
    - Avatrombopag, oral daily dose of 20–40 mg (dose adjustment with respect to other adult populations is not required).
    - Fostamatinib, start with two oral daily doses of 100 mg, increase to 150 mg if required to reach the target.
- Recommended option when there is high thromboembolic risk.
    - Rituximab, four doses of 100 or 375 mg/m2 for 4 consecutive weeks (long-term remissions are scarce, and toxicity is higher).

- Other options
    - Immunosuppressants or immunomodulators (if moderate disease): mycophenolate mofetil, cyclosporin, azathioprine, danazol, dapsone (well-characterized profiles of safety/efficacy).

Pregnant patients:

- Before making therapeutic decisions, the differential diagnosis must be carefully assessed in order to rule out other causes of thrombocytopenia, especially those which are pregnancy-related.
- Patients with platelet counts ≤20–30 x 10^9/L require treatment. To undergo delivery, the recommended target for platelet count is >50 x 10^9/L for vaginal and >70 x 10^9/L for cesarean or if epidural anesthesia is going to be used.
- First-line options:
    - Prednisone, 10–20 mg/day, using the lowest possible dose that is enough to reach platelet counts in the range of 20–30 x 10^9/L.
    - IVIg (daily dose of 1 g/kg for 2 days or daily dose of 0.4 g/kg for 5 days), in the event of prednisone-induced side effects, severe bleeding or requirement of rapid recovery of platelets to prepare for delivery.
- Other options
    - Azathioprine, cyclosporin. If splenectomy is decided (data regarding safety/efficacy are limited, risk of neonatal Thrombocytopenia), the procedure should be performed in the second trimester.
    - Management of neonates will depend on their platelet count values:
        - If these are <100 x 10^9/L, repeat on a daily basis.
        - If these are <50 x 10^9/L, perform cranial ultrasound. If hemorrhage is detected, administer IVIg and steroids, pursuing a platelet count target of >100 x 10^9/L. Although there is no evidence about what the most suitable steroid is, a short course of methylprednisolone could be a good option.
        - If these are <30 x 10^9/L or there are hemorrhagic symptoms, administer one single dose of IVIg (1 g/kg) to achieve rapid response.

Secondary ITP:

- The first-line treatment is similar in most cases of primary and secondary ITP, namely, glucocorticoids and/or IVIg. However, when choosing the second-line option, one has to consider seriously the underlying disease when managing secondary ITP.

Primary ITP in thrombosis:

- Thrombocytopenia is associated with a poorer prognosis in patients with acute coronary syndromes. Thus, platelet count recovery must be a priority target.
- Treatment must be individualized according to hemorrhagic history and thromboembolic risk. In an acute arterial episode with platelet counts > 10 x 10^9/L aspirin could be used, while double antiplatelet treatment may be considered with platelet counts > 30 x 10^9/L.
- Anticoagulants can be used at full doses with platelet counts > 50 x 10^9/L. With lower counts, the options are either dose reduction or suspension. In those situations where anticoagulation is contraindicated while immediate measures are required, a vena cava filter can be used or, with platelet counts < 10 x 10^9/L, prophylactic platelet transfusion could be performed.
- In patients with thromboembolic history, the preferred choices for first- and second-line treatment are glucocorticoids and fostamatinib, respectively. Only in the event of no response to the latter, if maintenance of the platelet count is required in order to continue administering antiplatelet or anticoagulant treatment safely, the use of TPO-RAs could be considered.

Primary ITP and COVID-19:

- Patients with platelet counts < 20 x 10^9/L and/or active bleeding have to be treated with prednisone, 0.5–1 mg/kg/day for no more than 2 weeks, with progressive reduction and suspension not beyond 8 weeks from the start.
- Those patients with severe COVID-19 who are already with corticoids and present with platelet counts < 20 x 10^9/L and/or active bleeding could be additionally treated with IVIg, 2 g/kg total doses. If counts < 20 x 10^9/L and/or active bleeding persist, one TPO-RA could be administered, although, at the lowest possible dose, Fostamatinib may be one alternative option to TPO-RA.
- Rituximab must be avoided, since the patient's ability to produce antibodies would be compromised. For the same reason, other immunosuppressants should also be avoided whenever possible.
- When patients with chronic primary ITP who are being well-controlled with treatment are infected by SARS-CoV-2, their therapeutic regimen should not be modified.
- In the event that the infection induces a relapse, IVIg should be administered in case of severe thrombocytopenia and, if bleeding occurred, a platelet transfusion could be performed. Those patients who are already under treatment with TPO-RA could consider either a dose increase or the addition of another TPO-RA or fostamatinib.

- If patients with primary ITP who are receiving anticoagulant/antiplatelet treatment are infected by SARS-CoV-2 and present with severe symptoms:
    - If they are on LMWH, they can continue treatment at full dose provided that platelet counts are >30 x 10^9/L.
    - If they are on other anticoagulant or antiplatelet agents, treatment at full dose could be administered with platelet counts > 50 x 10^9/L.
    - The risk of secondary ITP subsequent to SARS-CoV-2 vaccination is not higher than that induced by another antiviral vaccines; SARS-CoV-2 vaccine is not contraindicated in pregnant women or patients with history of ITP.

1.4 International Guidelines

1.4.1 Consensus Guidelines for the Management of Adult Immune Thrombocytopenia in Australia and New Zealand (2022)

This consensus statement has been endorsed by the Thrombosis and Haemostasias Society of Australia and New Zealand (THANZ) Council and ITP Australia. The guidelines recommendations are accompanied by a grading scheme, outlined as follows[8]:

Table 5. Australia and New Zealand 2022 Grading System Employed to Append Recommendations

Strength of Recommendation	
1	Strong
2	Weak
Quality of Supporting Evidence	
A	High quality meta-analysis
B	Robust phase 3 studies
C	Well-designed phase 2 studies, or good quality case series
D	Expert panel consensus

Treatment is recommended for newly diagnosed ITP when platelet counts are consistently < 20 × 10^9/L, even in the absence of bleeding (GRADE 1C).

If the patient has no or only mild bleeding and platelets > 20 × 10^9/L, then a watch-and-wait strategy is usually appropriate (GRADE 2C).

First line treatment

Steroids (usually prednisone and dexamethasone):

- Prednisone is recommended at a starting dose of 1 mg/kg/day for the first 2 weeks, followed by a tapering regimen over 6 weeks (GRADE 1C). Consider initially capping the dose to 75–80 mg once daily, even for patients weighing > 80kg (GRADE 2D).
- An alternative regimen is dexamethasone 40 mg or 0.6 mg/kg orally once daily for 4 days, every 14–28 days for one to six cycles (GRADE 1C).
- Some investigators report higher remission rates with pulsed dexamethasone as opposed to standard-dose prednisone, with fewer adverse effects.
- The dexamethasone dose can be attenuated to 20 mg for older patients (GRADE 2D).
- Patients requiring longer term steroid therapy (steroid-dependent after more than 8–10 weeks) or repeated courses of steroid therapy should be referred to a tertiary centre with experience in ITP (GRADE 2D).
- Prednisone is favored in older patients less likely to tolerate the neuropsychiatric side effects of dexamethasone. Dexamethasone is favored in those seeking a more rapid response with shorter overall duration of steroid exposure.

Intravenous immunoglobulin (IVIg):

- IVIg can be used periprocedurally as on-demand or as first line therapy in combination with steroids. The 5% and 10% formulations appear to have similar efficacy (response rates about 75%).
- Dosing options include 0.4 g/kg daily for 3–5 days or 1 g/kg for 1–2 days, with the latter option being associated with a faster response.
- Therapy with prednisone or dexamethasone can be combined with IVIg, or intravenous methylprednisolone can be substituted for the oral steroid, if there is a need for a more rapid response (GRADE 1C).
- Criteria permitting access to IVIg generally require thrombocytopenia < 30 × 10^9/L, the presence or perceived risk of bleeding, poor response to other therapies (steroids in newly diagnosed ITP or splenectomy in chronic ITP), and special clinical circumstances (pregnancy, periprocedural).

Second line treatments

- There is no consensus on which second line treatment for ITP should be attempted first.

- Patients should switch to a second line treatment when the first line treatment has not obtained a hemostatic response. The risk of bleeding and mortality increases with platelet counts < 20 × 10^9/L; hence, treatment is often aimed at achieving a platelet count > 20 × 10^9/L and avoidance of severe bleeding.
- Inadequate hemostatic response with > 5 mg/day of prednisone, three to four cycles of high dose dexamethasone, or with one or more courses of IVIg represent failure of first line treatment.
- Patient preferences, age, lifestyle, comorbidities, and drug availability are important when considering when to start a second line treatment and which treatment modality to adopt (GRADE 1D).
- Splenectomy, rituximab and thrombopoietin receptor agonists (TPO-RAs) have the most robust evidence in terms of efficacy and safety and hence it is recommended that these three options be discussed with patients as suitable second line treatments (GRADE 1C)
- It is agreed to postpone splenectomy for at least 12 months, since up to one-third of patients achieve satisfactory homeostatic response (either spontaneously or with treatment) (GRADE 1C). Therefore, for patients with ITP with a disease duration of less than 12 months, TPO-Ras and rituximab should be pursued as first choice second line treatment.
- **Vaccinations** against encapsulated bacteria Neisseria meningitidis, Streptococcus pneumoniae and Haemophilus influenzae should be administered before splenectomy and rituximab when possible (GRADE 1C). Postoperative thromboprophylaxis and antibiotic prophylaxis should be administered as per local and national guidelines for splenectomy, but patients with ITP are at a higher risk of thrombosis.
- **Splenectomy -** Patient selection:
    - Patients aged less than 65 years, with disease duration greater than 12 months, and for whom this option impacts least on their lifestyle (GRADE 2D).
    - Patients without a history of thrombosis or infections are favorable candidates for splenectomy (GRADE 2D).
- **Rituximab**:
    - Rituximab dosing regimens administered in ITP include 375 mg/m2/week for 4 weeks, 1 g rituximab on day 1 and day 15, and 100 mg/week for 4 weeks.

- Time to response has been reported to be slower in lower dose strategies, but there is no advantage in response rate with standard or higher dose regimens.
- Re-administration of rituximab can be considered in patients who have obtained an initial response of more than 12 months (GRADE 2C).
- Hepatitis B carrier status should be reviewed before treatment commencement due to the risk of reactivation (GRADE 1C).
- Vaccine responses can be suppressed by rituximab for up to 6 months; therefore, potential candidates for subsequent splenectomy in rituximab failure should be offered vaccinations before commencing rituximab therapy (GRADE 1D).
- **Patient selection**:
  - Rituximab should be considered in patients who have expressed a strong preference to avoid surgery. It is recommended to administer rituximab with high dose dexamethasone (up to three cycles) (GRADE 1C).
  - Rituximab is favored for patients without a concomitant immunodeficiency and for those at risk of thrombosis (GRADE 1D).
  - Rituximab should be considered in younger, female patients with short disease duration (< 1–2 years) (GRADE 2C).

- **TPO-RAs (eltrombopag and romiplostim):**
  - Eltrombopag is given once daily orally while romiplostim is dosed as a weekly subcutaneous injection.
  - Eltrombopag dosing starts at 50 mg daily (25 mg daily in East Asian people) and can be increased up to a maximum of 75 mg daily. Eltrombopag must be given on an empty stomach; in particular, it should be taken 4 hours after or 2 hours before products or food containing cations (calcium, dairy products, iron supplements).
  - Romiplostim dosing starts at 1 μg/kg/week, and can be increased up to a maximum of 10 μg/kg/week until a response is achieved. In cases where a rapid response is needed, the guidelines recommend starting with the contents of one small vial (250–375 μg), which is often approximately 3–4 μg/kg (GRADE 1D).
  - **Treatment-free response and discontinuation:**
    - Predictors for treatment-free response are not established; however, TPO-RAs discontinuation may be considered in

patients maintaining platelet responses > 50 × 10^9/L for more than 6–12 months, absence of previous major bleeding, and/or requiring only low doses of TPO-RAs (GRADE 2D).

- Given the risk of rebound thrombocytopenia, TPO-RAs discontinuation should not occur abruptly, but it should be done with a slow taper.
- it is recommended that discontinuation be delayed if there is a history of significant platelet count fluctuation, variable adherence to therapy, past major bleeding, or sudden relapse (GRADE 1D).
- Tapering to cessation can be commenced sooner if platelet counts are persistently above 200 × 10^9/L (GRADE 2D).

- **Patient selection:**
  - In Australia, TPO-RAs are approved for treatment of chronic ITP following splenectomy and inadequate response to IVIg, or in patients for whom splenectomy is contraindicated.
  - In New Zealand, TPO-RAs are approved as fourth line therapy after splenectomy or as third line therapy if splenectomy is contraindicated.
  - Romiplostim is recommended in patients with gastrointestinal diseases, abnormal liver function, or who are unable to adhere to prescribed dietary restrictions (GRADE 1D).
  - Eltrombopag is recommended in patients who have a needle phobia and in those who prefer the simplicity of once daily dosing (GRADE 1D).
  - Paradoxically, as eltrombopag can be difficult to administer effectively in an aged care environment due to the uncertainty of dose timing in relation to meal service, hence, romiplostim is recommended in this setting (GRADE 2D).

- **Other options -** Mycophenolate mofetil and dapsone**:**
  - Mycophenolate mofetil and dapsone are preferred in this setting, with a quicker onset of action compared with the other medications (GRADE 1C).
  - While these drugs are generally more accessible and affordable, evidence regarding efficacy is less robust. Their onset of action can be more prolonged than that of rituximab, splenectomy or TPO-RAs.

- In view of this, steroids are often administered concurrently with these medications while awaiting response, resulting in additional toxicity.
- Prolonged treatment may also be required, and alternative strategies should be quickly considered if toxicity is encountered.

Beyond second line therapies

- Clinical trial enrolment of eligible patients with ITP who have not responded to currently available therapies is strongly recommended where available in limited sites around Australia and New Zealand (GRADE 1D).
- Non-rescue low dose steroids, such as prednisolone ≤ 5 mg/day or 10 mg once a week, can be considered to improve the response to many second line therapies, including TPO-RAs (GRADE 2D).
- Combination therapy can also have a synergistic effect (e.g., TPO-RAs plus an immunosuppressant such as mycophenolate mofetil or azathioprine) (GRADE 2D).

Supportive care in ITP

- Management of acute bleeding, avoidance of long-term side effects of therapies (particularly steroids), and identification of fatigue.
- Acute bleeding management includes tranexamic acid (avoid if hematuria) and proton pump inhibitors in major gastrointestinal bleeding.
- Avoidance of long-term high dose steroid use in patients with ITP is imperative (GRADE 1B). Patients taking an equivalent of prednisolone 20 mg daily for more than 2 weeks are at increased risk of infection.
- Bone mineral density assessments should be considered for patients who have received prolonged steroids and are at risk of osteopenia, such as post-menopausal women, and they should be proactively managed with calcium and vitamin D supplements.
- Currently, PBS reimbursement exists for intravenous zoledronic acid 5 mg annually with corticosteroid-induced osteopenia (GRADE 2D).
- Fatigue appears common in patients with ITP, but its optimal management has not been ascertained. Referral to counselling and ITP-specific patient support networks may be helpful.
- Splenectomized patients should be reviewed for their risk of infection and thrombosis, adherence to local guidelines on long term antibiotic use, immunization status, and modifiable vascular risk factors (GRADE 1D).

Treatment of emergency bleeding in ITP

- In life-threatening bleeding, the guidelines recommend platelet transfusions to achieve hemostasis, along with IVIg (1–2 g/kg), and steroids (methylprednisolone up to 1000 mg intravenous daily for 1–5 days or high dose dexamethasone 40 mg daily intravenous or orally for 4 days) (Grade 1D).
- Vinka alkaloids can be considered for rare cases of refractory or multiply relapsed disease and life-threatening bleeding (GRADE 2D).
- Some authors have experience with using vincristine 1–2 mg intravenously (over 4–6 hours) weekly for two to four doses, and treatment effect can be seen in less than 48 hours.
- Supportive red cell transfusions, antifibrinolytic therapy with tranexamic acid (up to 1000 mg intravenous three times a day) and other blood products may be useful.
- Local measures such as endoscopic cautery need to be considered in gastrointestinal bleeding and epistaxis (GRADE 1D).
- Splenectomy for emergency bleeding is difficult given the dangers of unplanned surgery.

Therapeutic interventions to raise platelet counts before surgery or procedures

- For emergency procedures (within hours), IVIg (1 g/kg) with intravenous methylprednisolone (500–1000mg) should be given immediately (GRADE 1B), and platelet transfusion (at induction of anesthesia, and subsequently intra- and/or postoperatively depending on bleeding) should be given as close to the time of the procedure as possible or on induction of anesthesia, with expected platelet survival of 1–4 hours (GRADE 1C).
- It is recommended to not delay any procedure to confirm a platelet increment, as very little would be expected (GRADE 1D).
- Repeat doses of IVIg may be needed if postoperative bleeding risk remains high.
- For elective procedures (days to one week), options include IVIg (GRADE 1B), steroids (GRADE 1B), or TPO-RA (romiplostim 500 μg subcutaneous weekly for two doses; commencing 10 days before surgery) (GRADE 1D).

Pregnancy

- In the first and second trimesters, the indication for treatment is a platelet count < 20×10^9/L.

- For vaginal or Caesarean delivery, a platelet count ≥ 50 × 10^9/L is generally adequate.
- For women with platelet counts < 20 × 10^9/L, prednisone 50 mg daily could be considered (GRADE 2D).
- If IVIg is used before delivery or for life-threatening hemorrhage, the recommended dose is 1–2 g/kg as a single or divided dose (GRADE 1D).
- Patients may respond to the combination of steroids and IVIg if they do not respond to monotherapy.
- It is sometimes useful to rehearse ITP treatment several weeks before term, in order to plan for a neuraxial anesthesia, where a platelet target ≥ 70 × 10^9/L is reasonable (GRADE 2D).

Arterial disease and severe thrombocytopenia in ITP

- Second line immunosuppressive therapies may be more attractive, as splenectomy would be less likely to be safe in patients with vascular comorbidities, in addition to the inherent increased risk of thrombosis following splenectomy.
- After balancing the risk of vascular disease against the risk of bleeding, the clinician is advised to target the greater problem; if they are both unacceptable, the guidelines advise increasing ITP therapy to mitigate the risk of bleeding from treating the vascular disease (GRADE 2D).
- It is generally safe to administer antiplatelet therapy if platelet counts are ≥ 30 × 10^9/L, and dual antiplatelet therapy if platelet counts are ≥ 50 × 10^9/L (GRADE 1D).
- Bare metal stents may reduce the duration of antiplatelet therapy required and may be preferred in patients with unstable or refractory thrombocytopenia (GRADE 2D).
- Anticoagulation for atrial fibrillation can be considered when the likely benefits outweigh the risk of bleeding, and it is usually safe with platelet counts ≥ 50 × 10^9/L but may be individualized in patients without a history of thrombocytopenic bleeding down to 30 × 10^9/L (GRADE 1D).
- Platelet transfusions have no role in routinely supporting platelet counts for antiplatelet therapies or anticoagulation in patients with ITP (GRADE 1D).

Venous thromboembolic disease and severe thrombocytopenia in ITP

- Prophylactic doses of low molecular weight heparin are generally safe to administer with platelet counts ≥ 30 × 10^9/L (GRADE 1D).

- Therapeutic anticoagulation is generally safe to administer for VTE management with platelet counts ≥ 30 × 10^9/L, and reduced intensity (half dose) anticoagulation is probably safe for platelet counts 20–30 × 10^9/L (GRADE 1D).
- The duration of anticoagulation and selection of anticoagulant are mostly unaffected by ITP, although patients with unstable platelet counts or a history of recent bleeding may be safer on anticoagulants with reversibility such as vitamin K antagonists (warfarin) and dabigatran (GRADE 2D).
- There is increasing familiarity with direct oral anticoagulants, but these should be used with caution in patients with labile platelet counts.
- ITP therapy can be titrated to raise the platelet count for safer anticoagulation, but this should be balanced against the risk of provoking VTE (GRADE 2D).
- Prothrombotic ITP therapies (e.g., TPO-RA) can usually be continued while remaining on indefinite anticoagulation (GRADE 2D).
- After excluding other causes of VTE (e.g., antiphospholipid syndrome), strong consideration should be given to changing ITP therapies if the thromboembolic event was life-threatening (GRADE 1D).

1.4.2 Expert Report on Immune Thrombocytopenia: Current Diagnostics and Treatment – Recommendations from an Expert Group from Austria, Germany, and Switzerland (2023)

The following recommendations are meant to assist physicians, dentists, and other health-care professionals who do not often see ITP patients. The expert report is an update of the German ITP guidelines from 2018 to 2021[14].

Corticosteroids are immunosuppressive and the general opinion is that they inhibit the formation of platelet autoantibodies. They achieve an increase in platelet counts in most patients at least temporarily.

- Prednisone vs dexamethasone:
    - The decision to give predniso(lo)ne or dexamethasone should be left to the physician's discretion.
    - Dexamethasone is contraindicated for the treatment of ITP during pregnancy.
    - The usual dose of dexamethasone is 40 mg/d × 4 days every 2–4 weeks, 3 cycles (in studies, 1 to a maximum of 6 cycles).

    - Two randomized trials, though numbers of patients were small, showed more long-term remissions with first line dexamethasone than with prednisone.
    - Other studies found no difference but a faster response with dexamethasone and thus a lower overall steroid burden.
    - Cushingoid changes are not as common with dexamethasone as with predniso(lo)ne.
- 1st-Line Corticosteroid Monotherapy versus Corticosteroid Combinations:
    - First-line corticosteroid monotherapy achieves 30–50% stable, therapy-free remission. Attempts have been made to improve on this by combining corticosteroids with other agents.
    - The combination of corticosteroids with mycophenolate mofetil or with tacrolimus in first-line achieve 60–70% therapy-free remissions (follow-up time 1 year and longer) and thus significantly greater than corticosteroids alone. However, mycophenolate and tacrolimus are not approved for ITP, and their potential side effects might negatively impact patients' quality of life.
    - The authors do not anticipate that these new combinations will play a major role in first-line ITP therapy.
    - There are also data on the combination of corticosteroids with rituximab or TPO-RAs as first-line therapy. However, these studies are small; phase III data with higher patient numbers are eagerly awaited.
    - The use of rituximab or TPO-RAs in first-line ITP treatment is "off-label" and should be restricted to clinical trials.
- Achieving a Therapy-Free Remission with TPO-RAs:
    - Discontinuation of TPO-RAs should be attempted if the platelet count has been above 50,000/µL for 6 months or longer.
    - The TPO-RA dose is gradually decreased over several weeks. This strategy will be successful in approximately one-third of patients, and further therapy will not be required.
- New Therapies, Not Yet Licensed:
    - All-Trans-Retinoic Acid (ATRA, Vitamin A):
        - Because ATRA supports the function of T helper and T regulatory lymphocytes, it might correct immune dysregulation in patients with ITP.

        - ATRA has been evaluated both in combination with dexamethasone as first-line therapy of newly diagnosed ITP (dose 20 mg/d; 68% therapy-free remissions) and in combination with rituximab for chronic relapsed ITP (dose 20 mg/m2/d for 12 weeks, 61% therapy-free remissions).
        - ATRA is not currently licensed for the treatment of ITP.
    - Atorvastatin:
        - Atorvastatin has a stimulatory effect on megakaryocytes and thrombopoiesis in patients with steroid-refractory ITP. A clinical trial examining the combination of dexamethasone and atorvastatin in newly diagnosed ITP is underway (NCT03692754).
    - Oseltamivir:
        - One study showed that the combination of dexamethasone and oseltamivir was effective in achieving therapy-free remissions in newly diagnosed ITP patients.
        - Unfortunately, relapses were also reported in these patients.
    - Bruton's tyrosine kinase (BTK) inhibitors:
        - This pharmacological class is used to treat B-cell lymphomas, but because they also inhibit plasma cell antibody production and phagocytosis by macrophages, they might also be effective in immune diseases.
        - However, ibrutinib, acalabrutinib, and zanabrutinib, the BTK inhibitors currently approved for lymphoma treatment, inhibit platelet aggregation, and cause a mild bleeding tendency.
        - Therefore, these drugs are usually contraindicated in patients with thrombocytopenia.
        - Another BTK inhibitor, rilzabrutinib, has been studied in patients with chronic ITP and has no antiplatelet activity. A recent phase I/II study showed a greater than 50% response rate and only mild side effects (nausea, diarrhea, bloating, and fatigue).
        - A phase III trial (Luna 3) has been initiated, and another BTK inhibitor, orelabrutinib, is being investigated.
    - Daratumumab:
        - Clinical trials of daratumumab in ITP have been launched based on the concept that this agent might disable the long-lived autoreactive plasma cells in the bone marrow that account for

the failure of conventional treatments in autoimmune cytopenias (Dart study).

- Bortezomib:
  - There are case reports describing bortezomib-induced increases in platelet counts in patients with multidrug resistant ITP.
  - One theory is that bortezomib, as compared with rituximab and other immunosuppressants, has greater access to the long-lived plasma cells that produce platelet autoantibodies.
  - Alternatively, bortezomib might prevent dendritic cells from presenting antigens to CD4 lymphocytes.
- Decitabine:
  - There are some case reports suggesting that decitabine might correct immune dysregulation in ITP and promote megakaryocyte maturation.
- Inhibitors of the Neonatal Fc Receptor:
  - Rozanolixizumab and efgartigimod are FcRn antagonists that interfere with the IgG-FcRn binding and increase lysosomal degradation of normal IgG and disease-causing IgG autoantibodies.
  - Both agents have been studied in patients with chronic ITP and produce an increase in platelet counts.
  - Their side effects include headache, fever, and abdominal discomfort.
  - Positive phase III study results have currently been published for efgartigimod, but the ITP studies with rozanolixizumab have been discontinued for non-medical reasons.
- Inhibitors of B-Cell Activating Factor:
  - Belimumab also shows activity in chronic ITP. In the few patients treated to date, the response rate is 80%, including 66% complete remissions. Side effects include infusion reactions, mild symptoms of serum sickness, and mild infections.
- Sutimlimab:
  - In a phase I study of multi-refractory ITP patients, sutimlimab achieved a rapid increase in platelet counts in approximately half of the patients.

- Platelet counts declined when sutimlimab was discontinued.
- It is noteworthy that sutimlimab can rapidly and sustainably suppress fatigue in patients with autoimmune hemolysis and might also be beneficial for the fatigue suffered by many ITP patients.

Tables 6 and 7 detail the recommendations regarding the use of anticoagulation and antiplatelet therapies with thrombocytopenia:

Table 6. Recommendations on the Use of Anticoagulation Therapy in Thrombocytopenia

Platelets	Indication for anticoagulation		
	Venous thromboembolism	**Atrial fibrillation**	**Mechanical heart valve**
50–100,000/μL	Continue anticoagulation with usual dose. Consider LMWH if platelet levels fluctuate widely, even dropping below 50,000/μL		
25–50,000/μL	**Prophylactic anticoagulation** with LMWH only with high thrombotic risk. If platelet count cannot be raised → consider 50% of the regular prophylactic dose		
	Therapeutic anticoagulation for acute VTE with prophylactic or 50% dose-reduced LMWH	If platelet count cannot be raised and CHA2DS2VASC score ≥4 → consider left atrial appendage occlusion	Platelet counts 40–50,000/μL → adjust warfarin dose to target INR of 2, if feasible (low therapeutic range)

			Platelet counts 25–40,000/μL → half therapeutic dose of LMWH
<25,000/μL	If platelet count cannot be raised → stop anticoagulation		
	Consider IVC filter	Consider left atrial appendage occlusion	

Table 7. Recommendations for the Use of Antiplatelet Therapy in Thrombocytopenia

Platelet count	**Indication for antiplatelet therapy**	
	Single antiplatelet therapy with aspirin (or clopidogrel), e.g., after myocardial infarction, stroke, TIA, etc.	**Dual antiplatelet therapy, e.g., after coronary stent placement**
75–100,000/μL	Continue low-dose aspirin (or clopidogrel)	Dual antiplatelet therapy with aspirin and clopidogrel for 3–6 months. Avoid ticagrelor or prasugrel
50–75,000/μL	Continue low-dose aspirin (or clopidogrel) only in the absence of major bleeding risk factors	
25–50,000/μL	Withhold single agent antiplatelet therapy unless major/multiple cardiovascular risk factors without major bleeding risk factors	Low-dose aspirin only (no clopidogrel) unless major cardiovascular risk factors without other major bleeding risk factors
<25,000/μL	Stop single agent antiplatelet therapy	Avoid coronary intervention if possible. Low-dose aspirin only under very high-risk conditions and if platelets >10,000/μL

1.4.3 Korean Society of Hematology Guidelines on the Management of Immune Thrombocytopenia (2022)

These guidelines aimed to provide helpful recommendations for managing adult and pediatric patients with immune thrombocytopenic purpura (ITP). In addition, these guidelines aim to provide clinical support for the decision-making process regarding different treatment courses[10].

Management of adult patients with newly diagnosed ITP

- In adult patients with newly diagnosed ITP and a platelet count $<20\times10^9$/L without symptoms or with minor mucocutaneous bleeding, the authors recommend corticosteroids rather than observation.
- To choose corticosteroid versus observation, physicians should consider the level of platelet count, additional comorbidities, use of anticoagulant or antiplatelet agents, need for subsequent procedures, and patient age.
- In adult patients with newly diagnosed ITP and a platelet count $\geq20\times10^9$/L without symptoms or minor mucocutaneous bleeding, the authors recommend observation rather than corticosteroids.
- For patients with a platelet count at the lower end of this threshold, those with additional comorbidities, anticoagulant or antiplatelet agents, or need to follow the procedures. Corticosteroid treatment may be appropriate for elderly patients (aged $>$60 yr).
- The authors recommend a short course (≤6 wk) of prednisone rather than a prolonged course ($>$6 wk, including treatment and tapering).
- The authors recommend either prednisone (0.5–2.0 mg/kg/day) or dexamethasone (40 mg/day for 4 days) as the type of initial corticosteroid treatment. Dexamethasone may be preferable to prednisone, considering that the response at 7 days was more desirable with dexamethasone (dexamethasone had a faster platelet count response).
- The authors recommend corticosteroids alone rather than corticosteroids combined with rituximab as the initial treatment. An initial course of corticosteroids combined with rituximab may be preferable when the possibility of remission is higher than the concerns regarding the potential side effects of rituximab.

Management of adult patients with corticosteroid-dependent or refractory ITP

In adult patients with corticosteroid-dependent or refractory ITP for more than 3 months, the authors recommend a thrombopoietin receptor agonist (TPO-RA), either eltrombopag or romiplostim.

Physicians should consider the preferences of individual patients when choosing daily oral medications or weekly subcutaneous injections.

Based on the available evidence, it is presumed that there is no difference between the two treatments. Preference of the patients for the route of administration – oral daily medication compared with weekly subcutaneous injection– likely affects treatment decision-making.

Second line therapies

- In adult patients with ITP lasting ≥ 3 months who are corticosteroid-dependent or unresponsive to corticosteroids, the authors recommend TPO-RA rather than splenectomy.
- Splenectomy should be postponed for at least 12 months after diagnosis because of the possibility of spontaneous remission in the first year.
- For patients with ITP lasting > 12 months, a splenectomy can only be performed in those with limited indications.

Management of pediatric patients with newly diagnosed ITP

- In pediatric patients with newly diagnosed ITP without bleeding or with minor bleeding, observation rather than corticosteroids is recommended. The authors also recommend observation rather than intravenous immunoglobulin (IVIG) or anti-D immunoglobulin.
- The authors recommend 7 days or shorter courses of corticosteroids rather than longer than 7 days in pediatric patients with newly diagnosed ITP with non-life-threatening mucosal bleeding and diminished HRQoL. In addition, the authors recommend 2–4 mg/kg/day of prednisolone (maximum 120 mg/day) for 5–7 days, rather than 0.6 mg/kg/day of dexamethasone (maximum 40 mg/day) for 4 days.
- In pediatric patients with newly diagnosed ITP with non-life-threatening bleeding and diminished HRQoL, the authors recommend corticosteroids rather than anti-D immunoglobulins or IVIG.

Management of pediatric patients with ITP who are unresponsive to first-line treatment

- In pediatric patients with ITP with non-life-threatening mucosal bleeding and diminished HRQoL who do not respond to first-line treatment, the authors recommend using TPO-RAs rather than rituximab or splenectomy.
- In adult patients with ITP who respond to TPO-RAs, the authors recommend using the lowest dose of TPO-RAs, sufficient to maintain a platelet count ≥50×109/L.

Other treatments for adult patients with ITP

- **Rituximab:**
    - It is a monoclonal antibody against the CD20 antigen that targets the B cell-producing antibodies for platelets.
    - Rituximab is usually administered at 375 mg/m2 intravenously every 4 weeks.
    - In adults with ITP who fail to respond to TPO-RA or experience relapse after discontinuing TPO-RA, rituximab can be administered as a third-line therapy.
- **Azathioprine:**
    - It is administered at an oral dose of 50–200 mg/day in adult patients and is sometimes administered with danazol; however, there is little data to support an improved response to the combination.
    - It takes several months to have a full effect on ITP.
    - Azathioprine is one of the drugs deemed “safe” for patients with ITP in pregnancy, without increased risk of fetal malformation, and safe during lactation.
    - Major adverse events included nausea, infection, liver function abnormalities, neutropenia, and anemia.
- **Cyclophosphamide**:
    - It is an immunosuppressive agent to treat autoimmune disorders at low doses.
    - Cyclophosphamide is usually delivered as an oral dose of 50–200 mg/day for adult patients.
    - Major adverse events include bone marrow suppression, infection, infertility, secondary malignancies, and hemorrhagic cystitis.

    - However, its use is contraindicated during pregnancy and lactation.
- **Cyclosporine A:**
    - This drug's levels were adjusted by monitoring drug levels. However, the usual starting dose is 3–6 mg/kg/day, with a maximum dose of 200 mg for adult patients.
    - Major adverse events were gingival hyperplasia, hypertension, renal toxicity, and emesis.
    - Therefore, its use is contraindicated during pregnancy and lactation.
- **Danazol**:
    - It is usually administered at an oral dose of 200–800 mg/day in adults.
    - Its androgenic effects are related to major adverse events (especially in women), transaminitis, weight gain, acne, rash, mood changes, amenorrhea, and virilization.
    - Therefore, clinicians should perform liver function tests at least once a month.
    - However, it is contraindicated during pregnancy and lactation.
    - It has sometimes been used in combination with azathioprine, but there is little evidence to support the added benefits of this combination.
- **Dapsone**:
    - It is administered orally at 50–100 mg/day to both adult and pediatric patients.
    - The treatment was generally well-tolerated. However, mild hemolysis occurs in most patients, whereas significant hemolysis is less common.
    - Therefore, clinicians should monitor for the potential development of methemoglobin.
- **Mycophenolate mofetil:**
    - It is administered orally at 500–2,000 mg/day to adult patients.
    - Serious adverse events include diarrhea, neutropenia, anemia, and viral infections. Prolonged drug use increases the risk for malignancy and progressive multifocal leukoencephalopathy. It has also been associated with pure red aplasia.
    - It is a teratogen that should not be prescribed during pregnancy or lactation.

- **Vinca alkaloids**:
    - Patients can achieve a rapid response at 7 days with vincristine (1–2 mg per dose once weekly for 2–4 weeks in adult patients) or vinblastine (10 mg per dose once weekly for 1–3 weeks in adult patients).
    - Almost all patients experience adverse events, such as vincristine neuropathy, vinblastine- associated bone marrow suppression, constipation, hyponatremia, and infusion site vesication.
    - Vinca alkaloids are contraindicated in pregnancy and lactation.

1.5 Systematic Reviews & Meta-Analyses

Table 8 tackles a systematic review and meta-analysis issued in **2022-2023** for **Immune Thrombocytopenic Purpura.**

Table 8. ITP Systematic Reviews and Meta-Analyses

Study title	Author (year)	Primary Objective	Outcomes	Results
All-trans retinoic acid added to treatment of primary immune thrombocytopenia: a systematic review and meta-analysis	Yang et al. (2023)[15]	All-trans retinoic acid (ATRA) application is a novel treatment approach for primary immune thrombocytopenia (ITP). This study aimed to evaluate the efficacy and safety of ATRA in the treatment of ITP.	The **primary outcomes** were the pooled overall response rate (ORR) and complete response rate (CRR). **Secondary outcomes** included relapse rate and salvage treatment rate. **Safety outcome** was to evaluate the adverse events associated with the use of all-trans retinoic acid.	In the five observational studies, the **pooled overall response rate (ORR) and complete response rate (CRR) were 59.5%** (95% confidence interval [CI], 52.4-66.4%) and **20.6%** (95% CI, 14.3-27.6%), respectively. In the selected four RCTs, the **pooled odds ratios for sustained response rate**, **ORR, and CRR were 3.00** (95% CI, 1.97-4.57; P < 0.01), **3.21** (95% CI, 2.15-4.78; P < 0.01), and **2.12** (95% CI, 1.17-3.86; P = 0.01), respectively. ATRA was associated with a **reduction in relapse rate and salvage treatment rate** (odds ratio, 0.30; 95% CI, 0.18-0.50; P < 0.01; 0.36; 95% CI, 0.23-0.56; P < 0.01, respectively). The **pooled odds ratios for grade 1-2 dry skin, headache (or dizziness), and rash acneiform were 49.99** (95% CI, 16.05-155.67; P < 0.01), **1.75** (95% CI, 0.98-3.12; P = 0.06), and **0.37** (95% CI, 0.10-1.34; P = 0.13), respectively. **Conclusion**:

				This study suggests that ATRA may significantly improve the initial and long-term response of patients with ITP.
Efficacy and safety of cyclosporine-based regimens for primary immune thrombocytopenia: a systematic review and meta-analysis	Li et. al 2023[16]	To conduct a meta-analysis assessing the efficacy and safety of cyclosporine-based combinations for primary immune thrombocytopenia (ITP).	A performed comprehensive analysis of the overall response rate (ORR), **complete response (CR) rate, partial response (PR) rate, relapse rate, platelet count, and adverse drug reaction (ADR) rate.**	Seven studies (n = 418) were ultimately included. According to a fixed-effects model, cyclosporine-based combinations **improved the ORR and CR rate and reduced the relapse rate**. The **ADR rate was not increased** in the cyclosporine-based combination group. Cyclosporine-based regimens effectively **increased the platelet count**. **Subgroup analysis illustrated** that cyclosporine-based combinations were linked to **higher ORRs in both children** (odds ratio [OR] = 5.74, 95% confidence interval [CI] = 1.79-18.41) and adults (OR = 5.46, 95% CI = 2.48-12.02) and a **higher CR rate in adults** (OR = 2.97, 95% CI = 1.56-5.63). **Conclusion**: Cyclosporine exhibited efficacy in the treatment of ITP without increasing the risk of ADRs.

Section 2.0 Drug Therapy

2.1 Immunosuppressive Agents

2.1.1 Dexamethasone

Information on Dexamethasone are detailed in the table below[17]:

Table 9. Dexamethasone Drug Information

SCIENTIFIC NAME DEXAMETHASONE	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D69. 3
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. For severe bleeding with thrombocytopenia, give in combination with other therapies[17] Based on the Saudi Panel 2019 recommendations, it is recommended as 40 mg/day for 4 days (can be repeated monthly up to four cycles).[6]
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 immunosuppressive therapies, or other drugs to treat ITP 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 ITP (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 ITP
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. **Most serious:** Adrenal suppression (tertiary adrenal insufficiency), Cushing syndrome, hyperglycemia, apathy/depression, peptic ulcers, infections, osteoporosis, glaucoma and cataracts.
Drug Interactions*	**Category X:** Aldesleukin BCG (Intravesical) Brivudine Cladribine Desmopressin

	Disulfiram Fexinidazole Fusidic Acid (Systemic) Indium 111 Capromab Pendetide Lapatinib Macimorelin Methotrimeprazine Mifamurtide MiFEPRIStone Nadofaragene Firadenovec Natalizumab Ornidazole Pimecrolimus Rilpivirine Ritlecitinib Ruxolitinib (Topical) Secnidazole Simeprevir Tacrolimus (Topical) Talimogene Laherparepvec Tertomotide
Special Population	**Older adults:** Use with caution in elderly patients with the smallest possible effective dose for the shortest duration. **Pediatrics:** May affect growth velocity; growth should be routinely monitored in pediatric patients.
Pregnancy	Teratogenic effects: Pregnancy Category C 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. **Cardiovascular disease:** Use with caution in patients with heart failure 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. **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. **Hepatic impairment:** Use with caution in patients with hepatic impairment,

	including cirrhosis; long-term use has been associated with fluid retention. **Hepatitis B:** Reactivation may occur. **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. **Pheochromocytoma:** 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. **Renal impairment:** Use with caution in patients with renal impairment; fluid retention may occur. **Seizure disorders:** Use corticosteroids with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis. **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. **Thyroid disease:** Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid patients. **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. **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. **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 ITP 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 10. 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 ITP. They can be used in combination with immunosuppressive therapies or other drugs used in the management of ITP and its complications. Dexamethasone is given at 40 mg/day for 4 days (can be repeated monthly up to four cycles). 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 ITP (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.

2.1.2 Prednisone

Information on Prednisone are detailed in the table below[17]:

Table 11. Prednisone Drug Information

SCIENTIFIC NAME Prednisone	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D69. 3
Drug Class	Anti-inflammatory Agent
Drug Sub-class	Corticosteroids
ATC Code	H02AB07
Pharmacological Class (ASHP)	Systemic Corticosteroids
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral
Dose (Adult) [DDD]	Note: Goal of therapy is to provide a safe platelet count to prevent clinically important bleeding rather than normalization of the platelet count. For patients with severe bleeding, a pulse of dexamethasone or methylprednisolone is recommended; due to the short-term response associated with methylprednisolone, a prednisone taper may be required following pulse doses

	of methylprednisolone. For minor bleeding, prednisone is an appropriate initial therapy 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.[17] 0.5–2 mg/kg/day for 2–4 weeks, and taper once response is observed[6]
Maximum Daily Dose Adults	80 mg/day initially
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 immunosuppressive therapies, or other drugs to treat ITP 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 ITP (consultant hematologist)
PA (Prior Authorization)	N/A
QL (Quantity Limit)	The duration of treatment is decided following discussion with the consultant hematologist. Maximum daily dose is 80 mg/day
ST (Step Therapy)	Corticosteroids are recommended first line treatment for ITP
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. **Most serious:** Adrenal suppression (tertiary adrenal insufficiency), Cushing syndrome, hyperglycemia, apathy/depression, peptic ulcers, infections, osteoporosis, glaucoma, and cataracts.
Drug Interactions*	**Category X:** Aldesleukin BCG (Intravesical) Brivudine Cladribine Desmopressin Disulfiram Fexinidazole Fusidic Acid (Systemic) Indium 111 Capromab Pendetide Lapatinib Macimorelin Methotrimeprazine Mifamurtide MiFEPRIStone Nadofaragene Firadenovec Natalizumab Ornidazole Pimecrolimus Rilpivirine Ritlecitinib Ruxolitinib (Topical) Secnidazole Simeprevir Tacrolimus (Topical) Talimogene Laherparepvec Tertomotide
Special Population	**Older adults:** Use with caution in elderly patients with the smallest possible effective dose for the shortest duration.

	Pediatrics: May affect growth velocity; growth should be routinely monitored in pediatric patients.
Pregnancy	**Pregnancy associated**: Oral: Initial: 10 to 20 mg once daily. Adjust to the minimum effective dose to achieve response; generally, continue for at least 21 days, then taper to the minimum effective dose required to maintain platelet count to prevent major bleeding or 1 mg/kg/day for 2 weeks, followed by a gradual taper. **Fetal alloimmune thrombocytopenia (maternal administration):** Oral: 0.5 to 1 mg/kg/day. Dose is dependent upon gestational age and risk of fetal/neonatal intracranial hemorrhage and is administered in addition to immune globulin IV. Teratogenic effects: Pregnancy Category C 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. **Cardiovascular disease:** Use with caution in patients with heart failure 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. **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. **Hepatic impairment:** Use with caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention. **Hepatitis B:** Reactivation may occur. **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.

	Pheochromocytoma: 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. **Renal impairment:** Use with caution in patients with renal impairment; fluid retention may occur. **Seizure disorders:** Use corticosteroids with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis. **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. **Thyroid disease:** Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid patients. **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. **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.

	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 ITP 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 12. 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 T=ITP. They can be used in combination with immunosuppressive therapies or other drugs used in the management of ITP and its complications. Prednisone is given at 0.5–2 mg/kg/day for 2–4 weeks and taper once response is observed. 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 ITP (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.

2.1.3 Methylprednisolone

Information on Methylprednisolone are detailed in the table below[17]:

Table 13. Methylprednisolone Drug Information

SCIENTIFIC NAME Methylprednisolone	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D69. 3
Drug Class	Anti-inflammatory Agent
Drug Sub-class	Corticosteroids
ATC Code	H02AB04
Pharmacological Class (ASHP)	Systemic Corticosteroids
DRUG INFORMATION	
Dosage Form	Oral solution, solution for injection, tablet, powder, and solvent for solution for injection, suspension for injection, lyophilizate for solution for injection
Route of Administration	Oral, intramuscular, and intravenous use
Dose (Adult) [DDD]	Note: Goal of therapy is to provide a safe platelet count to prevent clinically important bleeding rather than normalization of the platelet count. Patients with severe bleeding (in combination with other treatments): IV (succinate): 1 g once daily for 3 doses and then stop (no taper). Note: Due to the short-term response, maintenance therapy with an oral glucocorticoid (e.g., prednisone) may be required[17]

	Pulse methylprednisolone is recommended by Saudi Panel 2019[6].
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 immunosuppressive therapies, or other drugs to treat ITP 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 ITP (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 ITP
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. **Most serious:** Adrenal suppression (tertiary adrenal insufficiency), Cushing syndrome, hyperglycemia, apathy/depression, peptic ulcers, infections, osteoporosis, glaucoma, and cataracts.
Drug Interactions*	**Category X:** Aldesleukin

	BCG (Intravesical) Brivudine Cladribine Desmopressin Disulfiram Fexinidazole Fusidic Acid (Systemic) Indium 111 Capromab Pendetide Lapatinib Macimorelin Methotrimeprazine Mifamurtide MiFEPRIStone Nadofaragene Firadenovec Natalizumab Ornidazole Pimecrolimus Rilpivirine Ritlecitinib Ruxolitinib (Topical) Secnidazole Simeprevir Tacrolimus (Topical) Talimogene Laherparepvec Tertomotide
Special Population	**Older adults:** Use with caution in elderly patients with the smallest possible effective dose for the shortest duration. **Pediatrics:** May affect growth velocity; growth should be routinely monitored in pediatric patients.
Pregnancy	Teratogenic effects: Pregnancy Category C 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. **Cardiovascular disease:** Use with caution in patients with heart failure 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. **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. **Hepatic impairment:** Use with caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention. **Hepatitis B:** Reactivation may occur. **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. **Pheochromocytoma:** 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. **Renal impairment:** Use with caution in patients with renal impairment; fluid retention may occur. **Seizure disorders:** Use corticosteroids with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis. **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. **Thyroid disease:** Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid patients. **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. **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. **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 ITP 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 14. 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 ITP. They can be used in combination with immunosuppressive therapies or other drugs used in the management of ITP and its complications. Pulse Methylprednisolone is recommended. 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 ITP (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.

2.1.4 Mycophenolate Mofetil

Information on Mycophenolate Mofetil is detailed in the table below[17]:

Table 15. 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)	D69. 3
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
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[18].

	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 corticosteroids, immunosuppressive or other ITP medications.
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)	This drug is recommended as alternative for patients who fail to respond to first-line therapy or relapse after the initial response for the management of ITP.
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 hypomagnesemia, abdominal pain, nausea, vomiting, anemia, leukopenia **Most serious**: Acute inflammatory syndrome, Bone marrow suppression, GI effects, Infection, Lymphoproliferative disorders, Pure red cell aplasia
Drug Interactions*	**Category X**: • Abrocitinib • Adenovirus (Types 4, 7) Vaccine • Baricitinib • BCG (Intravesical) • BCG Vaccine (Immunization) • Brivudine [INT] • Cholera vaccine

	• Cholestyramine Resin • Cladribine • Colesevelam • Colestipol • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Ebola Zaire Vaccine (Live) • Filgotinib • Influenza Virus Vaccine (Live/Attenuated) • Japanese Encephalitis Virus Vaccine (Live/Attenuated) • Measles, Mumps, and Rubella Virus Vaccine • Measles, Mumps, Rubella, and Varicella Virus Vaccine • Mumps Virus Vaccine • Nadofaragene Firadenovec • Natalizumab • Pimecrolimus • Poliovirus Vaccine (Live/Bivalent/Oral) • Poliovirus Vaccine (Live/Trivalent/Oral) • Rotavirus Vaccine • Ruxolitinib (Topical) • Smallpox Vaccine Live • Tacrolimus (Topical) • Talimogene Laherparepvec • Tertomotide • Tofacitinib • Typhoid Vaccine • Upadacitinib • Varicella Virus Vaccine • Yellow Fever Vaccine Zoster Vaccine (Live/Attenuated)
Special Population	**Older Adult** 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. 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 medications a 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. • Serious Infections • Malignancies: lymphoma and other malignancies, particularly of the skin • Embryo-fetal toxicity. Avoid if safer options available
REMS	REMS Drugs COVID-19 Safety Alert: to assure safe use: consider whether there 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 Immune 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 16. 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 is recommended as an alternative for patients who fail to respond to first-line therapy or relapse after the initial response for the management of ITP. Only physicians experienced in hematology should prescribe Mycophenolate Mofetil. It can be used in combination with corticosteroids or other ITP medications. 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 ITP. Limitations for the use of Mycophenolate Mofetil include serious infections and malignancies.

2.1.5 Cyclosporine

Information on Cyclosporine is detailed in the table below[17]:

Table 17. Cyclosporine Drug Information

SCIENTIFIC NAME CYCLOSPORINE	
SFDA Classification	Prescription
SFDA	N/A
US FDA	Off-label
EMA	No
MHRA	No
PMDA	Off label
Indication (ICD-10)	D69. 3
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]	Immune thrombocytopenia, refractory (off-label use): Oral: 2.5 to 3 mg/kg/day as monotherapy or in combination with other agents (e.g., prednisone)[17] Saudi panel 2019 recommended a dose of 2.5-5 mg/kg of body weight per day (dose to be adjusted by blood level, target 100-400 ng/ml)[6]
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. Kidney impairment prior to treatment initiation: no adjustment necessary. 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. 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 patients who fail to respond to first-line therapy or relapse after the initial response.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Hypertension, Hirsutism, Urinary tract infection, Tremor **Most serious:** • Diabetes mellitus • Drug-induced gingival overgrowth • Drug-induced thrombotic microangiopathy • Hepatotoxicity

	• Hyperkalemia • Hypertension • Infections • Malignancy • Nephrotoxicity • Neurotoxicity
Drug Interactions*	**<u>Category X:</u>** • Abrocitinib • Adenovirus (Types 4, 7) Vaccine • Aliskiren • AMILoride • Asunaprevir • Atorvastatin • Baricitinib • BCG (Intravesical) • BCG Vaccine (Immunization) • Bilastine Depends on Renal Function • Bosentan • Brivudine [INT] • Cholera Vaccine • Cladribine • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Disulfiram Depends on Dosage Form • DOXOrubicin Conventional • Dronedarone • Ebola Zaire Vaccine (Live) • Elagolix • Elagolix, Estradiol, and Norethindrone • Elbasvir and Grazoprevir • Eplerenone • Erdafitinib • Fexinidazole • Filgotinib • Foscarnet • Fusidic Acid (Systemic) • Grapefruit Juice Depends on Route

	• Influenza Virus Vaccine (Live/Attenuated) • Japanese Encephalitis Virus Vaccine (Live/Attenuated) • Lasmiditan • Lercanidipine • Lovastatin • Measles, Mumps, and Rubella Virus Vaccine • Measles, Mumps, Rubella, and Varicella Virus Vaccine • Methotrimeprazine Depends on Dosage Form • Mifamurtide • MiFEPRIStone Depends on Indication • Mumps Virus Vaccine • Nadofaragene Firadenovec • Natalizumab • Ornidazole Depends on Dosage Form and International labeling • Pacritinib • PAZOPanib • Pimecrolimus • Pimozide • Pitavastatin • Poliovirus Vaccine (Live/Bivalent/Oral) • Poliovirus Vaccine (Live/Trivalent/Oral) • Red Yeast Rice • Revefenacin • Rotavirus Vaccine • Ruxolitinib (Topical) • Secnidazole Depends on Dosage Form • Simeprevir • Simvastatin • Sirolimus (Protein Bound) • Smallpox Vaccine Live • Sparsentan

	• XSpironolactone • Tacrolimus (Systemic) • Tacrolimus (Topical) • Talimogene Laherparepvec • Taurursodiol • Tertomotide • Tofacitinib • Topotecan Depends on Route • Treosulfan • Triamterene • Typhoid Vaccine • Upadacitinib • Varicella Virus Vaccine • VinCRIStine (Liposomal) • Voxilaprevir • Yellow Fever Vaccine • Zavegepant • Zoster Vaccine (Live/Attenuated)
Special Population	Older Adult Considerations 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 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. 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 the patient is taking; alternative therapy or dosage adjustment may be needed. When transferring patients with previously 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. 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. • Immunosuppression • Erratic absorption and bioavailability • 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. • Hypertension/nephrotoxicity
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Immune Thrombocytopenic Purpura (ITP) 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 18. 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 patients who fail to respond to first-line therapy or relapse after the initial response. This drug is given as oral cyclosporine 2.5-5 mg/kg of body weight per day (dose to be adjusted by blood level). Blood levels of cyclosporine should be monitored to maintain a trough level of approximately 100–400 ng/mL. Only physicians experienced in immunosuppressive therapy and hematology should prescribe Cyclosporine. There are no HTA recommendations regarding the use of Cyclosporine in ITP. Limitations for the use of Cyclosporine include nephrotoxicity, hypertension, and psoriasis.

2.1.6 Azathioprine

Information on Azathioprine is detailed in the table below[17]:

Table 19. Azathioprine Drug Information

SCIENTIFIC NAME Azathioprine	
SFDA Classification	Prescription
SFDA	Yes for chronic refractory idiopathic thrombocytopenic purpura.
US FDA	Off label
EMA	Yes
MHRA	Yes
PMDA	No
Indication (ICD-10)	D69. 3
Drug Class	Immunosuppressant Agent
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]	Immune thrombocytopenia, chronic, refractory or relapsed (off-label use): Oral: 1 to 2 mg/kg/day; maximum dose: 150 mg/day. Initial response is observed at 30 to 90 days; may take up to 6 months for peak response.[17] Saudi Panel 2019 recommends 2 mg/kg oral daily.[6]
Maximum Daily Dose Adults	150 mg/day
Dose (pediatrics)	Immune thrombocytopenia (ITP), chronic refractory: 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:** **Altered kidney function:** *CrCl ≥30 mL/minute:* Initial: No dosage adjustment necessary *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) *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) *Hemodialysis, intermittent (thrice weekly)*: Dialyzable (45% removed 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 *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) *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. **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 once daily as an initial dose is recommended) *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. **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) **Hepatic Impairment: Adult** There are no dosage adjustments provided in the manufacturer's labeling. **Adjustment for Toxicity: Adult** *Rapid WBC count decrease, persistently low WBC count, or serious infection*: Reduce dose or temporarily withhold treatment. *Severe toxicity (hematologic or other) in kidney transplantation*: May require discontinuation.

	Hepatic sinusoidal obstruction syndrome (SOS; veno-occlusive disease): Permanently discontinue. *Rheumatoid arthritis*: Leukopenia and thrombocytopenia: Consider a 50% dose reduction or discontinuation; 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 ITP patients
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** o GI effects (nausea, vomiting, diarrhea) o Hematologic toxicity (leukopenia, thrombocytopenia, and anemias, including macrocytic anemia and/or pancytopenia) o 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) o Liver dysfunction o 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) o Pancreatitis
Drug Interactions*	**<u>Category X:</u>** • Abrocitinib • Baricitinib • BCG (Intravesical) • BCG products • Brivudine • Cladribine • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Dipyrone • Febuxostat • Fexinidazole • Filgotinib • Mercaptopurine • Mumps- Rubella- or Varicella-Containing Live Vaccines • Nadofaragene Firadenovec • Natalizumab • Pimecrolimus • Poliovirus Vaccine (Live/Trivalent/Oral) • Ritlecitinib • Ruxolitinib (Topical) • Tacrolimus (Topical) • Talimogene Laherparepvec

	• Tertomotide • Tofacitinib • Typhoid Vaccine • Upadacitinib • Vaccines (Live) • 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. 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 (e.g., cyclophosphamide, chlorambucil, melphalan) may have a prohibitive risk of malignancy with azathioprine treatment. 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 malignancy (e.g., splenomegaly, hepatomegaly, abdominal pain, persistent fever, night sweats, weight loss). Patients taking azathioprine for a prolonged time 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 Immune Thrombocytopenic Purpura (ITP) 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 20. Azathioprine HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Azathioprine	NICE	N/A
	CADTH	N/A
	HAS[13]	**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 patients who fail to respond to first-line therapy or relapse after the initial response. This drug is given as Oral: 2 mg/kg/day; 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 ITP except for the positive recommendation from HAS. Limitations for the use of Azathioprine include malignancy.

2.2 Immunoglobulins

2.2.1 Intravenous Immunoglobulin (IVIG)

Information on IVIG is detailed in the table below[17]

Table 21. IVIG Drug Information

SCIENTIFIC NAME IVIG	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D69. 3
Drug Class	Blood Product Derivative
Drug Sub-class	Immune Globulin
ATC Code	J06BA01
Pharmacological Class (ASHP)	Antitoxins and Immune Globulins
DRUG INFORMATION	
Dosage Form	Solution for infusion
Route of Administration	IV use
Dose (Adult) [DDD]	IvIg can be dosed in the following manner, **as per the Saudi panel 2019**: 1 g/kg/day for 1–2 days.[6] **Immune thrombocytopenia (adjunctive or alternative agent)**[17]:

	Note: For patients who require a rapid increase in platelet count, those who do not respond to glucocorticoids, and those who cannot tolerate glucocorticoids. IVIG may also be used for patients with critical bleeding or a need for urgent surgery or procedures (e.g., pregnancy). IV: 1 g/kg once daily for 1 or 2 days; second dose may be withheld if adequate platelet response (eg, platelets >50,000/mm3) in 24 hours. Alternative dosing: 400 mg/kg once daily for 5 days. **Fetal and neonatal alloimmune thrombocytopenia (maternal administration):** IV: 1 to 2 g/kg per week, with or without glucocorticoids (doses >1 g/kg are typically divided into 2 doses and given over 2 days). Dose is dependent upon gestational age and risk. **IV administration of Privigen 10%:** ITP: Initial: 0.5 mg/kg/minute (0.3 mL/kg/hour); Maintenance: Increase gradually (if tolerated) up to 4 mg/kg/minute (2.4 mL/kg/hour). Privigen: If necessary to further dilute, D5W may be used. Vials may be pooled into sterile infusion bags and infused; manufacturer's labeling for Privigen states infusion should begin within 8 hours after pooling.
Maximum Daily Dose Adults	N/A
Dose (pediatrics)	Privigen: Adolescents ≥15 years: Chronic therapy: IV: 1,000 mg/kg/dose once daily for 2 days.[17]
Maximum Daily Dose Pediatrics	N/A

Adjustment	**Dosing: Older Adult** Refer to adult dosing. Use with caution; administer the minimum dose and infusion rate practicable. **Dosing: Altered Kidney Function: Adult** IV: Use with caution due to risk of immune globulin-induced renal dysfunction; the rate of infusion and concentration of solution should be minimized. Discontinue if renal function deteriorates during treatment. IM: There are no dosage adjustments provided in the manufacturer's labeling. SUBQ infusion: There are no dosage adjustments provided in the manufacturer's labeling; consider lower, more frequent dosing. **Dosing: Hepatic Impairment: Adult** IM, IV, SUBQ infusion: There are no dosage adjustments provided in the manufacturer's labeling. **Dosing: Obesity: Adult** Class 1, 2, and 3 obesity (BMI ≥30 kg/m2): IV, SUBQ: Use adjusted body weight for weight-based dose calculations. Refer to adult dosing for indication-specific doses. **Dosing: Altered Kidney Function: Pediatric** IV: Use with caution due to risk of immune globulin-induced renal dysfunction; the rate of infusion and concentration of solution should be minimized. Discontinue if renal function deteriorates during treatment.

	IM: There are no dosage adjustments provided in the manufacturer's labeling. SubQ infusion: There are no dosage adjustments provided in the manufacturer's labeling; consider lower, more frequent dosing. **Dosing: Hepatic Impairment: Pediatric** IM, IV, SubQ infusion: There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits	MD, ST, CU, PA, AGE
AGE (Age Edit):	Use with caution in elderly patients; may be at increased risk for renal dysfunction/failure and thromboembolic events.
CU (Concurrent Use Edit):	Can be used in combination with steroids or other ITP medications.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	Only physicians experienced in immunosuppressive therapy and hematology should prescribe this drug.
PA (Prior Authorization):	This drug is recommended in ITP cases refractory to corticosteroids, when side effects to corticosteroids are significant, or when a rapid increase in platelets is needed. It can also be used in combination with steroids or other ITP medications. It is given as 1 g/kg/day for 1–2 days. Only physicians experienced in immunosuppressive therapy and hematology should prescribe this drug. Can induce a rapid response within 1–2 days and is therefore useful in emergency settings (ongoing bleeding, surgery). Use with caution in elderly patients; may be at increased risk for renal dysfunction/failure and thromboembolic events.
QL (Quantity Limit):	N/A

ST (Step Therapy):	This drug is recommended as an adjunctive or alternative treatment to steroids as first line therapy.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**<u>Most common: >10%:</u>** **Cardiovascular**: Chest pain, decreased heart rate, hypertension, hypotension, increased heart rate, tachycardia **Dermatologic**: Dermatitis, ecchymoses, injection site pruritus **Gastrointestinal**: Abdominal pain, diarrhea, nausea, upper abdominal pain, viral gastroenteritis, vomiting **Hematologic & oncologic**: Anemia, hemolysis, positive direct Coombs test **Hepatic**: Increased serum alanine aminotransferase, increased serum alkaline phosphatase, increased serum bilirubin (increased direct serum bilirubin or increased indirect serum bilirubin) **Immunologic**: Antibody development **Local**: Bruising at injection site, erythema at injection site, injection site nodule, irritation at injection site, pain at injection site, swelling at injection site **Nervous system**: Chills, dizziness, fatigue, headache, increased body temperature, pain, rigors **Neuromuscular and skeletal**: Asthenia, back pain, limb pain, myalgia **Respiratory**: Asthma, bronchitis, cough, epistaxis, nasal congestion, nasopharyngitis, pharyngitis, rhinitis, sinusitis (including acute sinusitis), upper respiratory tract infection, wheezing **Miscellaneous**: Fever

Drug Interactions	No reported Category X interactions
Special Population	**Older adult:** Use with caution in elderly patients; may be at increased risk for renal dysfunction/failure and thromboembolic events.
Pregnancy	IVIG has been recommended for use in fetal-neonatal alloimmune thrombocytopenia and pregnancy-associated immune thrombocytopenia (ITP); use is appropriate for ITP in cases refractory to corticosteroids, when side effects to corticosteroids are significant, or when a rapid increase in platelets is needed. Human IgG crosses the placenta. Fetal exposure is dependent upon the IgG subclass, maternal serum concentrations, placental integrity, newborn birth weight, and GA, generally increasing as pregnancy progresses. The lowest exposure would be expected during the period of organogenesis and the highest during the third trimester. In a study of 2 women treated with IV immune globulin (IVIG) for common variable immunodeficiency, exogenous immune globulin was shown to cross the placenta similar to endogenous immune globulin.
Lactation	Immune globulin is endogenous to breast milk. Human immune globulin concentrations are dependent upon IgG subclass and postpartum age. In a study of 2 women treated with IV immune globulin for common variable immunodeficiency, the colostrum of one mother with IgA deficiency was

	found to provide similar IgA immunological protection as mothers without a deficiency. 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. Immune globulin is considered compatible with breastfeeding.
Contraindications	Hypersensitivity to immune globulin or any component of the formulation; IgA deficiency (with anti-IgA antibodies and history of hypersensitivity; and hyperprolinemia.
Monitoring Requirements	Renal function (prior to initial infusion and at appropriate intervals), urine output, IgG concentrations, hemoglobin and hematocrit, platelets (in patients with ITP); infusion- or injection-related adverse reactions, anaphylaxis, signs and symptoms of thrombosis, signs and symptoms of hemolysis; blood viscosity (in patients at risk for hyperviscosity); presence of antineutrophil antibodies (if TRALI is suspected); volume status; neurologic symptoms (if AMS suspected); pulmonary adverse reactions; blood pressure (prior to, during, and following infusion); clinical response. **For patients at high risk of hemolysis (dose ≥2 g/kg, given as a single dose or divided over several days, and non-O blood type):** Hemoglobin or hematocrit prior to and 36 to 96 hours post-infusion and again at 7 to 10 days post-infusion.

	SUBQ infusion: For treatment of primary humoral immunodeficiency, monitor IgG trough levels every 2 to 3 months before/after conversion from IV; subcutaneous infusions provide more constant IgG levels than usual IV immune globulin treatments.
Precautions	**Concerns related to adverse effects:** **Anaphylaxis/hypersensitivity reactions:** Hypersensitivity and anaphylactic reactions can occur (some severe); patients with known antibodies to IgA are at greater risk; a severe fall in blood pressure may rarely occur with anaphylactic reaction; discontinue therapy and institute immediate treatment (including epinephrine 1 mg/mL) should be available. **Aseptic meningitis:** Aseptic meningitis syndrome (AMS) has been reported with immune globulin administration; may occur with high doses (≥1 g/kg) and/or rapid infusion. Syndrome usually appears within several hours to 2 days following treatment; usually resolves within several days after product is discontinued. Female patients or patients with a migraine history may be at higher risk for AMS. **Hematoma:** Do not administer subcutaneously for the treatment of immune thrombocytopenia because of the risk of hematoma formation. **Hemolysis:** Intravenous immune globulin has been associated with antiglobulin hemolysis (acute or delayed). Cases of hemolysis-related

	renal impairment/failure or disseminated intravascular coagulation have been reported. Risk factors associated with hemolysis include high doses (≥2 g/kg) given either as a single administration or divided over several days, underlying associated inflammatory conditions, and non-O blood type (FDA 2012). An underlying inflammatory state (eg, elevated C-reactive protein or erythrocyte sedimentation rate) may also increase the risk. Closely monitor patients for signs of hemolytic anemia, particularly in patients with preexisting anemia and/or cardiovascular or pulmonary compromise. **Hereditary fructose intolerance:** Immune globulin may contain sorbitol. The presence of sorbitol presents a risk to those with hereditary fructose intolerance (HFI). The incidence of HFI is estimated at 1 in 20,000 births and is usually diagnosed at the time of weaning when fructose or sucrose is introduced into the diet. Clinical symptoms include recurrent vomiting, abdominal pain, and hypoglycemia. Immune globulin containing sorbitol must not be administered to patients with HFI. **Hyperproteinemia:** Hyperproteinemia, increased serum viscosity, and hyponatremia may occur; distinguish hyponatremia from pseudohyponatremia to prevent volume depletion, a further increase in serum viscosity and a higher risk of thrombotic events.

Hypertension: Elevations of blood pressure (systolic ≥180 mm Hg and/or diastolic >120 mm Hg) have been observed during and/or shortly following infusion of Privigen, which resolved with either observation or changes in oral antihypertensive therapy.

Infusion reactions: Patients should be monitored for adverse events during and after the infusion. Stop administration with signs of infusion reaction (fever, chills, nausea, vomiting, and rarely shock). Risk may be increased with initial treatment, when switching brands of immune globulin, and with treatment interruptions of >8 weeks.

Pulmonary edema: Monitor for transfusion-related acute lung injury (TRALI); noncardiogenic pulmonary edema has been reported with immune globulin use. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, and fever in the presence of normal left ventricular function. Usually occurs within 1 to 6 hours after infusion.

Renal dysfunction and acute renal failure: [US Boxed Warning]: IV administration only: Acute renal dysfunction (increased serum creatinine, oliguria, acute renal failure, osmotic nephrosis) can rarely occur and has been associated with fatalities in predisposed patients. Patients predisposed to renal dysfunction include elderly patients, patients with

	renal disease, diabetes mellitus, hypovolemia, volume depletion, sepsis, paraproteinemia, and nephrotoxic medications due to risk of renal dysfunction. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. (Note: Privigen do not contain sucrose). In patients at risk of renal dysfunction or acute renal failure, ensure adequate hydration prior to administration; the dose, rate of infusion, and concentration of solution should be minimized. Assess renal function prior to treatment and periodically thereafter. Discontinue if renal function deteriorates. **Thromboembolic events:** [US Boxed Warning]: Thrombosis may occur with immune globulin products even in the absence of risk factors for thrombosis. For patients at risk of thrombosis (eg, advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors), administer at the minimum dose and infusion rate practicable. Ensure adequate hydration before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity, such as those with cryoglobulins, fasting chylomicronemia/severe hypertriglyceridemia, or monoclonal gammopathies.

	Disease-related concerns: **Fluid overload:** High-dose regimens (1 g/kg for 1 to 2 days) are not recommended for individuals with fluid overload or where fluid volume may be of concern. **Renal impairment:** Use with caution; ensure adequate hydration prior to administration; the rate of infusion and concentration of solution should be minimized.
Black Box Warning	Thrombosis Renal dysfunction and acute renal failure
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Immune Thrombocytopenic Purpura (ITP) 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 IVIG.**

Table 22. IVIG HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
IVIG	NICE	N/A
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- IVIG

This drug is recommended in ITP cases refractory to corticosteroids, when side effects to corticosteroids are significant, or when a rapid increase in platelets is needed. It can also be used in combination with steroids or other ITP medications. It is given as 1 g/kg/day for 1–2 days. Only physicians experienced in

immunosuppressive therapy and hematology should prescribe this drug. Can induce a rapid response within 1–2 days and is therefore useful in emergency settings (ongoing bleeding, surgery). Use with caution in elderly patients; may be at increased risk for renal dysfunction/failure and thromboembolic events. There are no HTA recommendations regarding its use in ITP. Limitations for the use of IVIG include hypersensitivity reactions, AMS, hematoma, hemolysis, hereditary fructose intolerance, hyperproteinemia, hypertension, pulmonary edema, fluid overload, renal dysfunction and acute renal failure, and thrombosis.

2.2.2 Specific Immunoglobulin: Anti-D Immunoglobulin

Information on Anti-D immunoglobulin is detailed in the table below[17]

Table 23. Anti-D immunoglobulin Drug Information

SCIENTIFIC NAME **Anti-D immunoglobulin**	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes
EMA	Yes
MHRA	No
PMDA	No
Indication (ICD-10)	D69. 3
Drug Class	Blood product derivative
Drug Sub-class	Immunoglobulin
ATC Code	J06BB01
Pharmacological Class (ASHP)	N/A
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	IV use
Dose (Adult) [DDD]	Note: Calculate weight-based dosing for ITP using kilograms not pounds; calculations using pounds will result in a significant overdose. Rhophylac: IV: 50 mcg/kg WinRho SDF: IV: **Initial**:

	○ Hemoglobin ≥10 g/dL: 50 mcg/kg as a single injection, or can be given as 2 divided doses on separate days. ○ Hemoglobin 8 to <10 g/dL: 25 to 40 mcg/kg, as a single injection, or can be given as 2 divided doses on separate days. ○ Hemoglobin <8 g/dL: Alternative treatment should be used. **Maintenance**: Note: Dosing frequency determined by clinical response in platelet counts, RBC, hemoglobin, and reticulocyte levels. ○ Hemoglobin ≥10 g/dL: 50 to 60 mcg/kg ○ Hemoglobin 8 to <10 g/dL: 25 to 40 mcg/kg ○ Hemoglobin <8 g/dL: Alternative treatment should be used.
Maximum Daily Dose Adults	N/A
Dose (pediatrics)	Note: Most newly diagnosed patients can be managed with a watch and wait approach. If treatment is necessary, Rho(D) immune globulin is recommended as first-line in Rh-positive, non-splenectomized pediatric patients: **Infants (limited data available), Children, and Adolescents:** Initial treatment: IV: 50 to 75 mcg/kg (250 to 375 units/kg) as a single dose. Serious or life-threatening bleeding: IV: 75 mcg/kg (375 units/kg) as a single dose in combination with platelet infusion(s) and corticosteroids.

	Product-specific dosing: WinRho SDF: Children and Adolescents <16 years: **Initial**: o Hemoglobin <8 g/dL: Alternative therapy should be used. o Hemoglobin 8 to <10 g/dL: IV: 25 to 40 mcg/kg (125 to 200 units/kg) as single dose or divided into 2 doses given on separate days. o Hemoglobin ≥10 g/dL: IV: 50 mcg/kg (250 units/kg) as single dose or divided into 2 doses given on separate days. **Subsequent doses**: Note: Dosing frequency determined by clinical response in platelet count, hemoglobin, red blood cell counts, and reticulocyte levels; platelet counts >50,000/mm3 rarely require treatment. o Hemoglobin <8 g/dL: Alternative therapy should be used. o Hemoglobin 8 to 10 g/dL: IV: 25 to 40 mcg/kg (125 to 200 units/kg). o Hemoglobin >10 g/dL: IV: 50 to 60 mcg/kg (250 to 300 units/kg).
Maximum Daily Dose Pediatrics	N/A
Adjustment	**Dosing: Older Adult** Refer to adult dosing. Patients >65 years of age with a concurrent comorbid condition may be at increased risk of developing acute hemolytic reactions. Fatal outcomes associated with IVH have occurred most frequently in those >65 years. Use with caution; consider starting at lower doses. **Dosing: Altered Kidney Function: Adult and pediatric**

	There are no dosage adjustments provided in the manufacturer's labeling; use with caution. **WinRho SDF:** Administer at the minimum infusion rate possible and ensure adequate hydration prior to administration in patients with kidney function impairment. **Dosing: Hepatic Impairment: Adult and pediatric** There are no dosage adjustments provided in the manufacturer's labeling. **Dosing: Adjustment for Toxicity: Adult** **Hypersensitivity or allergic reaction**: Discontinue Rho(D) immune globulin immediately and manage appropriately. **Transfusion-related acute lung injury**: Manage with oxygen and adequate ventilatory support.
Prescribing edits	MD, ST, CU, PE, PA
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	Can be used in combination with systemic steroids or other ITP medications.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	Only physicians experienced in immunosuppressive therapy and hematology should prescribe this drug.
PA (Prior Authorization):	This drug is not advised in patients with active bleeding causing a decline in hemoglobin or those with evidence of autoimmune hemolysis. Use of Anti-D is limited to Rh +ve patients who have an acceptable hemoglobin level and a functional spleen. It can also be used in combination with systemic steroids or

	other ITP medications. Dosing regimen is based on the hemoglobin levels. Use of Anti-D is limited to Rh +ve patients who have an acceptable hemoglobin level and a functional spleen, and in patients who are refractory to steroid therapy or when side effects to corticosteroids are significant. Only physicians experienced in immunosuppressive therapy and hematology should prescribe this drug.
QL (Quantity Limit):	N/A
ST (Step Therapy):	Use of Anti-D is limited to Rh +ve patients who have an acceptable hemoglobin level and a functional spleen, and in patients who are refractory to steroid therapy or when side effects to corticosteroids are significant.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	Dosing regimen is based on the hemoglobin levels.
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** **>10%:** **Central nervous system:** Chills (5% to 35%), headache (11% to 14%) **Hepatic:** Increased serum bilirubin (21%) **Neuromuscular & skeletal:** Asthenia (3% to 11%) **Miscellaneous:** Fever (5% to 31%)
Drug Interactions	No reported Category X interactions
Special Population	N/A
Pregnancy	Available evidence suggests that Rho(D) immune globulin administration during pregnancy does not harm the fetus or affect future pregnancies. In pregnant patients who require treatment for immune thrombocytopenia (ITP), agents other

	than RhIG are preferred. RhIG may be used for refractory ITP in pregnant nonspelnectomized patients in the second and third trimester (limited data); monitor neonate for jaundice, anemia, and direct antiglobulin test positivity
Lactation	The purified immune globulin in these products is obtained from human donors; the Rho(D) antibodies are endogenous to human plasma. Adverse events in the breastfeeding infant have not been observed when administered to patients for the suppression of RhD isoimmunization. According to the manufacturer, the decision to continue or discontinue breastfeeding during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.
Contraindications	**Rhophylac:** Anaphylactic or severe systemic reaction to a previous dose of human immune globulin; use in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity to Rhophylac or any component of the formulation; administration to the neonate of a mother who received Rhophylac postpartum. **WinRho SDF:** Hypersensitivity to Rho(D) immune globulin or any component of the formulation; known anaphylactic or severe systemic reaction to a previous dose of human immune globulin; use in IgA-deficient patients with antibodies to IgA; autoimmune hemolytic anemia with preexisting hemolysis or at high

	risk for hemolysis; suppression of RhD isoimmunization in infants. **WinRho SDF Canadian labeling:** RhD alloimmunization prevention (pregnancy and other obstetric conditions): Hypersensitivity to Rho(D) immune globulin or any component of the formulation; known anaphylactic or severe systemic reaction to a previous dose of human immune globulin; RhD-positive patients; RhD- negative patients who are immunized; use in IgA-deficient patients; patients with antibodies to IgA or history of IgA hypersensitivity. Immune thrombocytopenia (ITP): Hypersensitivity to Rho(D) immune globulin or any component of the formulation; known anaphylactic or severe systemic reaction to a previous dose of human immune globulin; use in IgA-deficient patients; patients with antibodies to IgA or history of IgA hypersensitivity; RhD-negative patients; splenectomized patients; ITP secondary to other conditions including leukemia, lymphoma, or active viral infections with EBV or HCV; elderly patients with underlying cardiac, renal, or hepatic comorbidities that would predispose them to acute hemolytic reactions; autoimmune hemolytic anemia (Evan syndrome); systemic lupus erythematosus (SLE); antiphospholipid antibody syndrome.
Monitoring Requirements	Monitor for at least 8 hours following administration for signs and symptoms of intravascular hemolysis (IVH), including anemia, renal insufficiency,

	back pain, shaking, chills, discolored urine, or hematuria. For patients with suspected IVH, monitor post-treatment plasma hemoglobin, haptoglobin, LDH, and plasma bilirubin (direct and indirect). Monitor for transfusion-related acute lung injury (TRALI), infusion- or injection-related adverse reactions, and anaphylaxis. In addition, CBC (prior to therapy and 1 to 3 days after first infusion); differential and peripheral blood smear (prior to therapy), direct antiglobulin test and antibody screen (prior to therapy); reticulocyte count (prior to therapy); urinalysis (prior to therapy and 1 to 2 hours after treatment [product labeling specifies dipstick urinalysis at baseline and 2, and 4 hours prior to the end of the monitoring period]); serum creatinine and BUN (prior to therapy; monitor after therapy if post treatment hemoglobin decreases by >1 g/dL). Consider a baseline assessment of blood viscosity in patients at risk for hyperviscosity.
Precautions	**Concerns related to adverse effects:** **Anaphylactoid/hypersensitivity reactions**: Severe hypersensitivity reactions may occur. Immediate treatment (including epinephrine 1 mg/mL) for anaphylactoid and/or hypersensitivity reactions should be available during use. If symptoms of allergic or early signs of hypersensitivity reactions occur, discontinue immediately and institute appropriate treatment. **Anaphylaxis**: May contain trace amounts of IgA; patients with antibodies to IgA have a greater risk of

	developing potentially anaphylactic reactions. **Intravascular hemolysis**: Rhophylac, WinRho SDF: May cause fatal intravascular hemolysis (IVH) in RhD-positive patients treated with IV Rho(D) immune globulin for immune thrombocytopenia (ITP). IVH may result in clinically compromising anemia and multiorgan system failure including acute respiratory distress syndrome. Acute renal insufficiency, renal failure, severe anemia, and disseminated intravascular coagulation (DIC) have also been reported. Patients should be closely monitored and instructed to notify health care provider of signs/symptoms of IVH (back pain, shaking chills, fever, and discolored urine or hematuria). Absence of these signs and/or symptoms within 8 hours does not indicate IVH cannot occur. Previous administration of IV Rho(D) immune globulin does not preclude the possibility of IVH. Complications may occur more frequently in elderly patients with comorbid conditions and in patients with predisposing conditions. Use alternative therapies in patients with preexisting hemolysis or a high risk of hemolysis (eg, positive direct antiglobulin test, elevated reticulocyte count). Transfuse patients with hemolysis and clinically compromising anemia after receiving Rho(D) immune globulin; use RhD-negative packed red blood cells. **Pulmonary edema**: Monitor for adverse pulmonary events including

	transfusion-related acute lung injury (TRALI); noncardiogenic pulmonary edema has been reported with intravenous immune globulin (IVIG). TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, and fever in the presence of normal left ventricular function and usually occurs within 1 to 6 hours after infusion; may be managed with oxygen and respiratory support. **Renal effects**: Acute renal dysfunction/failure, acute tubular necrosis, osmotic nephropathy, proximal tubular nephropathy, and death may occur with IGIV products. Use with caution in patients with renal impairment or at risk for renal disease (eg, diabetes mellitus, >65 years of age, volume depletion, sepsis, paraproteinemia, concomitant use of nephrotoxic medications); administer at the minimum infusion rate possible and ensure adequate hydration prior to administration in these patients. **Thrombotic events**: Thrombotic events have been reported with administration of IVIG; use with caution in patients with a history of atherosclerosis, known/suspected hyperviscosity, advanced age, impaired cardiac output, prolonged immobilization, coagulation disorders, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, or multiple cardiovascular risk factors. Consider a baseline assessment of blood viscosity in patients at risk for hyperviscosity. Administer at the minimum practical

	infusion rate in patients at risk for thrombotic events. **Disease-related concerns:** **Bleeding/coagulation disorders**: Bleeding/hematoma may occur from IM administration. **Immune thrombocytopenia**: Although Rho(D) immune globulin is not the preferred pharmacologic agent for the management of immune thrombocytopenia, a single dose may be used in nonsplenectomized children who are RhD-positive and require treatment, or in adults when corticosteroids are contraindicated.
Black Box Warning	Intravascular hemolysis in immune thrombocytopenia
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Immune Thrombocytopenic Purpura (ITP) 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 Anti-D immunoglobulin.**

Table 24. Anti-D immunoglobulin HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Anti-D immunoglobulin	NICE	N/A
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Anti-D immunoglobulin

This drug is not advised in patients with active bleeding causing a decline in hemoglobin or those with evidence of autoimmune hemolysis. Use of Anti-D is limited to Rh +ve patients who have an acceptable hemoglobin level and a functional spleen. It can also be used in combination with systemic steroids or other ITP medications. Dosing regimen is based on the hemoglobin levels. Use of Anti-D is limited to Rh +ve patients who have an acceptable hemoglobin level and a functional spleen, and in patients who are refractory to steroid therapy or when side effects to corticosteroids are significant. Only physicians experienced in immunosuppressive therapy and hematology should prescribe this drug.
There are no HTA recommendations regarding its use in ITP. Limitations for the use of IVIG include hypersensitivity reactions, intravascular hemolysis, pulmonary edema, renal dysfunction and acute renal failure, and thrombosis.

2.3 Monoclonal Antibodies

2.3.1 Anti-CD20: Rituximab

Information on Rituximab is detailed in the table below[17]:

Table 25. Rituximab Drug Information

SCIENTIFIC NAME RITUXIMAB	
SFDA Classification	Prescription
SFDA	N/A
US FDA	No
EMA	No
MHRA	No
PMDA	Yes
Indication (ICD-10)	D69. 3
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]	Alternative agent (off-label use): Note: May be used as a single agent for patients who do not have an adequate platelet count response to glucocorticoids. Use in combination with other therapies has also been reported. Optimal dose, frequency, and duration have not been established and vary based on institutional protocols. IV: 375 mg/m2 once weekly for 4 doses. Safety: Administer appropriate immunizations prior (eg, ≥4 weeks) to starting therapy (if possible) and screen for active or latent infections. Avoid use in patients with severe active infection. Prophylaxis against opportunistic infection and/or viral reactivation may be warranted during and up to 12 months after completion of rituximab therapy. Manufacturer's labeling recommends premedicating ~30 minutes prior to administration with acetaminophen, an antihistamine, and methylprednisolone 100 mg IV (or equivalent). For uses requiring concomitant administration with a glucocorticoid, administer glucocorticoid component prior to rituximab infusion. Premedication practice may vary; refer to institutional protocols.
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.

	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. 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 steroid therapy or other ITP medications.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	Rituximab must be prescribed by a consultant hematologist for ITP.
PA (Prior Authorization):	Rituximab is considered as an alternative for patients who fail to respond to first-line therapy or relapse after the initial response for the management of ITP. This drug is given as 375 mg/m2 IV once weekly for 4 doses and can be used as monotherapy or in combination with steroids or other ITP medications. Rituximab must be prescribed by a consultant hematologist for ITP.
QL (Quantity Limit):	N/A
ST (Step Therapy):	Rituximab is considered as an alternative for patients who fail to respond to first-line therapy or relapse after the initial response for the management of ITP.
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 **Most serious**: • Hepatitis B virus reactivation • Hypogammaglobulinemia and Infection • Infusion-related reactions • Progressive multifocal leukoencephalopathy (PML)
Drug Interactions	**Category X:** • Abatacept • Abrocitinib • Adalimumab • Adenovirus (Types 4, 7) Vaccine • Anakinra • Anifrolumab • Baricitinib • BCG (Intravesical) • BCG Vaccine (Immunization) • Belimumab • Brivudine [INT] • Certolizumab Pegol • Cholera Vaccine • Cladribine • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Dipyrone • Ebola Zaire Vaccine (Live) • Etanercept • Fexinidazole • Filgotinib • Golimumab • InFLIXimab • Influenza Virus Vaccine (Live/Attenuated)

	• Japanese Encephalitis Virus Vaccine (Live/Attenuated) • Measles, Mumps, and Rubella Virus Vaccine • Measles, Mumps, Rubella, and Varicella Virus Vaccine • Mumps Virus Vaccine • Nadofaragene Firadenovec • Natalizumab • Pimecrolimus • Poliovirus Vaccine (Live/Bivalent/Oral) • Poliovirus Vaccine (Live/Trivalent/Oral) • Rotavirus Vaccine • Ruxolitinib (Topical) • Sarilumab • Smallpox Vaccine Live • Tacrolimus (Topical) • Talimogene Laherparepvec • Tertomotide • Tocilizumab • Tofacitinib • Typhoid Vaccine • Upadacitinib • Varicella Virus Vaccine • Yellow Fever Vaccine • 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. **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 gastrointestinal tract following exposure via breast milk.
Contraindications	There are no contraindications listed in the manufacturer's US labeling. 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 • **Cytopenias**: Rituximab is associated with lymphopenia, leukopenia, neutropenia, thrombocytopenia, and anemia; the duration of cytopenias may be prolonged and may extend months beyond treatment. • **Renal toxicity**: May cause fatal renal toxicity in patients with non-Hodgkin lymphomas (NHL). • **Tumor lysis syndrome** leading to acute renal failure requiring dialysis (sometimes fatal) may occur within 12 to 24 hours following the first dose when used as a single agent in the treatment of NHL. • **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. • **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. • Some dosage forms may contain polysorbate 80 (also known as Tweens). Hypersensitivity reactions, usually a delayed reaction, have been reported. • **Immunizations**: In the oncology setting, live vaccines should not be given before or during rituximab treatment
Black Box Warning	• Infusion-related reactions • Mucocutaneous reactions • Hepatitis B virus reactivation: some cases resulting in fulminant hepatitis, hepatic failure, and death. • Progressive multifocal leukoencephalopathy
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Immune 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 26. 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 an alternative for patients who fail to respond to first-line therapy or relapse after the initial response for the management of ITP. This drug is given as 375 mg/m2 IV once weekly for 4 doses, and can be used as monotherapy or in combination with a systemic steroid or other ITP medications. Rituximab must be prescribed by a consultant hematologist for ITP. There are no HTA recommendations for its use in ITP. Limitations for the use of Rituximab include infusion related reactions, hepatitis B virus reactivation, and Progressive Multifocal Leukoencephalopathy.

2.4 Thrombopoietin Receptor Agonists (TPO-RAs)

2.4.1 Eltrombopag

Information on Eltrombopag is detailed in the table below[17]

Table 27. Eltrombopag Drug Information

SCIENTIFIC NAME Eltrombopag	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D69. 3
Drug Class	Thrombopoietin Receptor Agonist
Drug Sub-class	Colony Stimulating Factor; Hematopoietic Agent; Thrombopoietic Agent
ATC Code	B02BX05
Pharmacological Class (ASHP)	N/A
DRUG INFORMATION	
Dosage Form	Film-coated tablet
Route of Administration	Oral use
Dose (Adult) [DDD]	It is recommended as 25-75 mg orally daily continuous therapy, as per the Saudi panel 2019 recommendations[6].

	Immune thrombocytopenia (persistent or chronic)[17]: Note: Use the lowest dose to achieve and maintain platelet count ≥50,000/mm3 as needed to reduce the risk of bleeding. Discontinue eltrombopag if platelet count does not respond to a level that avoids clinically important bleeding after 4 weeks at the maximum of 75 mg/day. Initial: Oral: 50 mg once daily (25 mg once daily for patients of East/Southeast Asian ancestry); dose should be titrated based on platelet response. Maximum dose: 75 mg/day. Dosage adjustment based on platelet response: Platelet count <50,000/mm^3 (≥2 weeks after treatment initiation or a dose increase): Increase daily dose by 25 mg (if taking 12.5 mg once daily, increase dose to 25 mg once daily prior to increasing the dose amount by 25 mg daily); maximum: 75 mg/day. Platelet count ≥200,000/mm^3 and ≤400,000/mm3 (at any time): Reduce daily dose by 25 mg (if taking 25 mg once daily, decrease dose to 12.5 mg once daily); reassess in 2 weeks. Platelet count >400,000/mm^3: Withhold dose; assess platelet count twice weekly; when platelet count <150,000/mm3, resume with the daily dose reduced by 25 mg (if taking 25 mg once daily, resume with 12.5 mg once daily).

	Platelet count >400,000/mm^3 after 2 weeks at the lowest dose: Discontinue treatment.
Maximum Daily Dose Adults	Maximum of 75 mg/day.
Dose (pediatrics)	**Chronic immune (idiopathic) thrombocytopenia (ITP): Note:** Use the lowest dose to achieve and maintain platelet count ≥50,000/mm^3 as needed to reduce the risk of bleeding. Discontinue if platelet count does not respond to a level that avoids clinically important bleeding after 4 weeks at the maximum daily dose of 75 mg. Initial: Children 1 to <6 years: Initial: Oral: 25 mg once daily (no dosage adjustment required for patients of East/Southeast Asian ancestry). Children ≥6 years and Adolescents: Initial: Oral: 50 mg once daily; for patients of East/Southeast Asian ancestry (eg, Chinese, Japanese, Korean, Taiwanese), reduce initial dose to 25 mg once daily. Dosage adjustment based on platelet response: Adjust dose to achieve/maintain platelet count ≥50,000/mm3 as necessary to reduce bleeding risk; maximum daily dose: 75 mg/day. Monitor platelet count weekly until stabilizes and then monthly; additional monitoring may be necessary based on response or any changes in product formulation (oral suspension/tablets).

	If platelet count <50,000/mm3 (≥2 weeks after treatment initiation or a dose increase): Increase daily dose by 25 mg (if taking 12.5 mg once daily, increase dose to 25 mg once daily prior to increasing the dose amount by 25 mg/day; maximum daily dose: 75 mg/day once daily. If platelet count ≥200,000/mm3 and ≤400,000/mm3 (at any time): Reduce daily dose by 25 mg (if previous dose 25 mg once daily, decrease dose to 12.5 mg once daily); reassess platelet count in 2 weeks. If platelet count >400,000/mm3: Withhold doses; assess platelet count twice weekly; when platelet count <150,000/mm3, resume with the daily dose reduced by 25 mg (if previous dose 25 mg once daily, resume with 12.5 mg once daily). If platelet count >400,000/mm3 after 2 weeks at the lowest dose: Discontinue treatment.
Maximum Daily Dose Pediatrics	Maximum daily dose: 75 mg/day once daily.
Adjustment	**Dosing: Older Adult** Refer to adult dosing. **Dosing: Altered Kidney Function: Adult** No dosage adjustment is necessary. **Dosing: Hepatic Impairment: Adult** **Adjustment for hepatic impairment prior to initiating treatment:**

	Immune thrombocytopenia: Note: In patients with immune thrombocytopenia (ITP) and hepatic impairment, wait 3 weeks (instead of 2 weeks) after therapy initiation or subsequent dosage changes prior to increasing dose. Mild, moderate, or severe impairment (Child-Pugh classes A, B, or C): Initial: 25 mg once daily. Patients of East/Southeast Asian ancestry with hepatic impairment (Child-Pugh classes A, B, or C): Initial: Consider 12.5 mg once daily. **Adjustment for hepatotoxicity during treatment:** **ITP:** ALT levels ≥3 times the ULN in patients with normal hepatic function or ≥3 times baseline (or >5 times ULN, whichever is lower) in those with preexisting transaminase elevations and which are progressive, persistent (≥4 weeks), accompanied by increased direct bilirubin, or accompanied by clinical signs of liver injury or evidence of hepatic decompensation: Discontinue treatment. Hepatotoxicity may recur with re-treatment after therapy interruption, but if determined to be clinically beneficial, may cautiously resume treatment; monitor ALT weekly during dosage titration; permanently discontinue if liver function test elevations persist, worsen, or recur.
Prescribing edits	QL, MD, ST, PA, AGE, CU
AGE (Age Edit):	Eltrombopag has been approved for children with cITP who are aged 1 year or older

CU (Concurrent Use Edit):	It can be used with steroids therapy or other ITP medications.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	Only physicians experienced in immunosuppressive therapy and hematology should prescribe this drug.
PA (Prior Authorization):	This drug is recommended for patients who fail to respond to first-line therapy or relapse after the initial response. the TPO-RAs class are likely to become the preferred second-line option, once they are widely available because of the efficacy and favorable safety profile. Eltrombopag has also been approved for children with cITP who are aged 1 year or older. It is given for adults as 25-75 mg orally daily, continuous therapy. Maximum daily dose: 75 mg/day once daily. It can also be given in combination with steroid therapy or other ITP medications. Only physicians experienced in immunosuppressive therapy and hematology should prescribe this drug.
QL (Quantity Limit):	Maximum daily dose: 75 mg/day once daily.
ST (Step Therapy):	This drug is recommended for patients who fail to respond to first-line therapy or relapse after the initial response. the TPO-RAs class are likely to become the preferred second-line option, once they are widely available because of the efficacy and favorable safety profile.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**<u>Most common:</u>** **<u>>10%:</u>** **Hepatic**: Abnormal hepatic function tests (adults: 11%)

	Respiratory: Upper respiratory tract infection (children and adolescents: 17%; adults: 7%), nasopharyngitis (children and adolescents: 12%)
Drug Interactions	**Category X:** • Asunaprevir • Deferiprone • Elagolix • Elagolix, Estradiol, and Norethindrone • Elbasvir and Grazoprevir • PAZOPanib • Revefenacin • Taurursodiol • Topotecan • Voxilaprevir • Zavegepant
Special Population	N/A
Pregnancy	Patients who could become pregnant should use effective contraception (methods that result in <1% pregnancy rates) during eltrombopag therapy and for at least 7 days after the last eltrombopag dose. Thrombopoietin (TPO) receptor agonists are not currently a preferred treatment of immune thrombocytopenia during pregnancy; use may be considered in very serious cases when other therapies have failed. If a TPO receptor agonist is needed, an agent other than eltrombopag is preferred.
Lactation	It is not known if eltrombopag is present in breast milk. Due to the potential for serious adverse effects in the breastfed infant, breastfeeding is not recommended by the manufacturer.

Contraindications	There are no contraindications listed in the manufacturer's US labeling. Canadian labeling: Hypersensitivity to eltrombopag or any component of the formulation; severe hepatic impairment (Child-Pugh class C)
Monitoring Requirements	**Immune thrombocytopenia:** CBC with differential and platelet count (weekly at initiation and during dosage titration(s), then monthly when stable; after cessation, monitor weekly for ≥4 weeks; when switching between the oral suspension and tablet, monitor platelet counts weekly for 2 weeks, then monthly when stable). LFTs, including ALT, AST, and bilirubin (baseline, every 2 weeks during dosage titration(s), then monthly after a stable dose is achieved; repeat abnormal LFTs within 3 to 5 days; if confirmed abnormal, monitor weekly until abnormalities resolve, stabilize, or return to baseline). Obtain bilirubin fractionation (for elevated bilirubin). If re-treating after therapy interruption for hepatotoxicity (if potential treatment benefits outweigh risks), monitor LFTs weekly during dosage adjustment phase.
Precautions	**Concerns related to adverse effects:** **Cataract formation:** Cataract formation or worsening has been observed with eltrombopag; most patients had preexisting risk factors for cataracts, including corticosteroid use. **Hepatotoxicity:** Eltrombopag may increase the risk of severe and potentially life-threatening hepatotoxicity. Liver enzyme elevations may occur; drug-induced liver injury has

	been reported. Eltrombopag inhibits UGT1A1 and OATP1B1, which may lead to indirect hyperbilirubinemia; obtain fractionation for elevated bilirubin levels. Hepatotoxicity may recur with re-treatment after therapy interruption. **Thromboembolism:** Thrombotic/thromboembolic complications may occur with increases in platelet levels with eltrombopag. Complications including venous or arterial events were observed at low and normal platelet counts. Consider the potential for an increased risk of thromboembolism with eltrombopag in patients with known risk factors for thromboembolism (eg, factor V Leiden, ATIII deficiency, antiphospholipid syndrome, chronic liver disease). To minimize the risk for thrombotic complications, do not use eltrombopag in an attempt to normalize platelet counts; follow dosage adjustment recommendations to achieve/maintain target platelet counts. Thrombotic events, primarily involving the portal venous system, were more commonly seen in eltrombopag-treated patients with chronic hepatitis C with thrombocytopenia (when compared to placebo). Thrombotic events (including portal venous thrombosis) were also reported in a study of non-immune thrombocytopenia (ITP) thrombocytopenic patients with chronic liver disease undergoing elective invasive procedures receiving eltrombopag 75 mg once daily. Symptoms of portal vein thrombosis include abdominal pain, nausea,

	vomiting, and diarrhea. The risk for portal venous thrombosis is increased in thrombocytopenic patients with chronic liver disease receiving 75 mg once daily for 2 weeks as preparation for invasive procedures. **Disease-related concerns:** **Chronic hepatitis C infection:** May increase risk of hepatic decompensation when used in combination with interferon and ribavirin in patients with chronic hepatitis C. In clinical trials, patients with low albumin (<3.5 g/dL) or a Model for End-Stage Liver Disease (MELD) score ≥10 at baseline had an increased risk of hepatic decompensation; closely monitor these patients during therapy. Indirect hyperbilirubinemia is commonly observed with eltrombopag when used in combination with peginterferon and ribavirin. In addition, ascites, encephalopathy, and thrombotic events were reported more frequently than placebo in chronic hepatitis C trials. **Myelodysplastic syndromes:** Eltrombopag is not indicated for the treatment of myelodysplastic syndromes (MDS). A clinical trial comparing the combination of azacitidine plus eltrombopag to azacitidine plus placebo in patients with intermediate-1, intermediate-2, or high-risk MDS with thrombocytopenia was terminated due to lack of efficacy and for safety concerns (including increased progression to acute myeloid leukemia [AML]). Increased relative risks of death

	and progression to AML in the eltrombopag arm compared to placebo were observed in the study.
Black Box Warning	Hepatotoxicity
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Immune Thrombocytopenic Purpura (ITP) 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 Eltrombopag.**

Table 28. Eltrombopag HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Eltrombopag	NICE[19]	**26 October 2018** **Positive recommendation:** Eltrombopag is recommended within its marketing authorization as an option for treating chronic immune (idiopathic) thrombocytopenia purpura: • In adults who have had a splenectomy and whose condition is refractory to other treatments (for example, corticosteroids or immunoglobulins) or • As second-line treatment, in adults who have not had a splenectomy because surgery is contraindicated. And • If the manufacturer provides eltrombopag with the discount agreed in the patient access scheme.
	CADTH	N/A
	HAS[20]	**05 February 2020** **Positive recommendation:**

		Favorable opinion for maintenance of reimbursement in primary immune thrombocytopenia (ITP) lasting 6 months or longer from diagnosis and refractory to other treatments (e.g. corticosteroids, immunoglobulins).
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Eltrombopag

This drug is recommended for patients who fail to respond to first-line therapy or relapse after the initial response. the TPO-RAs class are likely to become the preferred second-line option, once they are widely available because of the efficacy and favorable safety profile. Eltrombopag has also been approved for children with cITP who are aged 1 year or older. It is given for adults as 25-75 mg orally daily, continuous therapy. Maximum daily dose: 75 mg/day once daily. It can also be given in combination with steroid therapy or other ITP medications. Only physicians experienced in immunosuppressive therapy and hematology should prescribe this drug.

There are two positive HTA recommendations favoring the use of Eltrombopag in chronic ITP, HAS and NICE, as mentioned in the above table. Limitations for the use of Eltrombopag include cataract formation, hepatotoxicity, thrombosis, and chronic hepatitis C infection.

2.4.2 Avatrombopag

Information on Avatrombopag is detailed in the table below[17]

Table 29. Avatrombopag Drug Information

SCIENTIFIC NAME Avatrombopag	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D69. 3
Drug Class	Thrombopoietin Receptor Agonist

Drug Sub-class	Colony Stimulating Factor; Hematopoietic Agent; Thrombopoietic Agent
ATC Code	B02BX08
Pharmacological Class (ASHP)	N/A
DRUG INFORMATION	
Dosage Form	Film-coated tablet
Route of Administration	Oral use
Dose (Adult) [DDD]	Oral: Note: Use the lowest dose necessary to achieve platelets count ≥50,000/mm3 as necessary to reduce the risk of bleeding. Initial: 20 mg once daily. Dosage adjustment based on platelet count: Avatrombopag dose levels for dose titration in chronic immune thrombocytopenia: o Dose level 6: 40 mg once daily. o Dose level 5: 40 mg 3 times per week and 20 mg/day on the other 4 days of the week. o Dose level 4: 20 mg once daily (initial dose for all patients except those taking moderate or strong dual inhibitors or inducers of CYP2C9 and CYP3A4). o Dose level 3: 20 mg 3 times per week. o Dose level 2: 20 mg twice per week or 40 mg once per week. o Dose level 1: 20 mg once weekly. Avatrombopag dosage adjustment in chronic immune thrombocytopenia (see above for dose levels):

	• Platelet count <50,000/mm3 after ≥2 weeks of avatrombopag: Increase dose one dose level; wait 2 weeks to reassess for subsequent dosage adjustments. • Platelet count 200,000/mm3 to 400,000/mm3: Decrease dose one dose level; wait 2 weeks to reassess for subsequent dosage adjustments. • Platelet count >400,000/mm3: Withhold avatrombopag and increase platelet monitoring to twice per week; when platelet count is <150,000/mm3, reinitiate avatrombopag with the dose decreased one dose level. • Platelet count <50,000/mm3 after 4 weeks of avatrombopag at 40 mg once daily: Discontinue avatrombopag. • Platelet count >400,000/mm3 after 2 weeks of avatrombopag at 20 mg once weekly: Discontinue avatrombopag. Avatrombopag discontinuation in chronic immune thrombocytopenia: Discontinue avatrombopag if the platelet count does not increase to ≥50,000/mm^3 after 4 weeks of therapy at the maximum dose of 40 mg once daily or if the platelet count is >400,000/mm3 after 2 weeks of therapy at 20 mg once weekly. Dosage adjustment for concomitant therapy: Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information.

Maximum Daily Dose Adults	Maximum dose of 40 mg once daily
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics	N/A
Adjustment	**Dosing: Older Adult** Refer to adult dosing. **Dosing: Altered Kidney Function: Adult** CrCl ≥30 mL/minute: There are no dosage adjustments provided in the manufacturer's labeling; however, mild to moderate renal impairment had no clinically meaningful effects on avatrombopag pharmacokinetics. **CrCl <30 mL/minute:** There are no dosage adjustments provided in the manufacturer's labeling (has not been studied). **Hemodialysis:** There are no dosage adjustments provided in the manufacturer's labeling (has not been studied); however, hemodialysis is not expected to enhance avatrombopag elimination. **Dosing: Hepatic Impairment: Adult** **Mild, moderate, or severe hepatic impairment (Child Pugh classes A, B, or C or MELD score 4 to 23):** There are no dosage adjustments provided in the manufacturer's labeling; however, hepatic impairment had no clinically meaningful effects on avatrombopag pharmacokinetics.
Prescribing edits	QL, MD, ST, CU, AGE, PA
AGE (Age Edit):	This drug is approved for adult population. Not studied in pediatrics

CU (Concurrent Use Edit):	Can be used with steroid therapy or other ITP medications.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	Only physicians experienced in immunosuppressive therapy and hematology should prescribe this drug.
PA (Prior Authorization):	This drug is recommended for patients who fail to respond to first-line therapy or relapse after the initial response. the dosing regimen is based on platelet count. Maximum dose of 40 mg once daily. This drug is approved for adult population. Not studied in pediatrics. I can also be used in combination with steroid therapy or other ITP medications. Only physicians experienced in immunosuppressive therapy and hematology should prescribe this drug. The dosing regimen is based on platelet count.
QL (Quantity Limit):	Maximum dose of 40 mg once daily
ST (Step Therapy):	Recommended for patients who fail to respond to first-line therapy or relapse after the initial response
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** **>10%:** **Gastrointestinal**: Gingival hemorrhage (13%) **Hematologic & oncologic**: Bruise (26%), petechia (11%) **Nervous system**: Fatigue (3% to 28%), headache (7% to 31%) **Neuromuscular & skeletal**: Arthralgia (13%) **Respiratory**: Epistaxis (19%), upper respiratory tract infection (15%)

	Miscellaneous: Fever (11%)
Drug Interactions	**No reported Category X interactions.**
Special Population	N/A
Pregnancy	Based on findings from animal reproduction studies, in utero exposure to avatrombopag may cause fetal harm. Thrombopoietin (TPO) receptor agonists are not currently recommended to treat immune thrombocytopenia during pregnancy except in very serious cases. If a TPO receptor agonist is needed, an agent other than avatrombopag is preferred.
Lactation	It is not known if avatrombopag is present in breast milk. Due to the potential for serious adverse events in the breastfed infant, the manufacturer does not recommend breastfeeding during chronic therapy or for ≥2 weeks after the last avatrombopag dose. If receiving avatrombopag for brief periods (eg, prior to an invasive procedure), lactating females should pump and discard breast milk during treatment and for ≥2 weeks after the last avatrombopag dose.
Contraindications	There are no contraindications listed in the manufacturer's labeling.
Monitoring Requirements	Platelet count weekly initially until stabilized at ≥50,000/mm3 then monthly thereafter. Obtain platelet count weekly for ≥4 weeks following discontinuation of therapy. All patients: Monitor for signs/symptoms of thromboembolism. Monitor adherence.
Precautions	**Concerns related to adverse effects:**

	Thromboembolism: Thrombotic and thromboembolic complications with thrombopoietin receptor agonist use have occurred. Portal vein thrombosis has occurred (rarely) in patients with chronic liver disease who received avatrombopag. Arterial and venous thrombotic events have occurred in patients with chronic immune thrombocytopenia. Use with caution in patients with known risk factors for thromboembolism (eg, Factor V Leiden, prothrombin 20210A, antithrombin deficiency, protein C or S deficiency). Do not administer to patients in an attempt to normalize platelet counts. Monitor for signs/symptoms of thromboembolism. **Dosage form specific issues:** **Lactose:** Dosage form contains lactose monohydrate. **Other warnings/precautions:** **Appropriate use:** Do not use to normalize platelet counts in patients with chronic liver disease or chronic immune thrombocytopenia. **CYP2C9 polymorphisms:** CYP2C9*2 and CYP2C9*3 loss-of-function polymorphisms result in reduced CYP2C9 enzymatic activity. In a pooled pharmacogenomic analysis, when compared to subjects wild-type for CYP2C9 (normal metabolizers), subjects heterozygous for CYP2C9 loss-of-function polymorphisms (intermediate metabolizers) experienced ~1.4-fold higher exposure, and subjects homozygous for CYP2C9 loss-of-function polymorphisms (poor

	metabolizers) had ~2-fold higher exposure.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Immune Thrombocytopenic Purpura (ITP) 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 Avatrombopag.**

Table 30. Avatrombopag HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Avatrombopag	NICE[21]	**15 December 2022** **Positive recommendation** Avatrombopag is recommended, within its marketing authorization, as an option for treating primary chronic immune thrombocytopenia (ITP) refractory to other treatments (for example, corticosteroids, immunoglobulins) in adults.
	CADTH[22]	**November 2023** **Negative recommendation** The CADTH Canadian Drug Expert Committee (CDEC) recommends that avatrombopag not be reimbursed for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.
	HAS[23]	**20 January 2021** **Negative recommendation** Unfavorable opinion for reimbursement in the treatment of severe

		thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo an invasive procedure.
	IQWIG[24]	**29 June 2021** **No data** In its dossier, the company did not submit any suitable data for assessing any added benefit of avatrombopag in adult patients with primary chronic ITP who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) in comparison with the ACT specified by the G-BA. Consequently, there is no hint of added benefit of avatrombopag in comparison with the ACT; an added benefit is therefore not proven.
	PBAC	N/A

CONCLUSION STATEMENT- Avatrombopag

This drug is recommended for patients who fail to respond to first-line therapy or relapse after the initial response. The dosing regimen is based on platelet count. Maximum dose of 40 mg once daily. This drug is approved for adult population. Not studied in pediatrics. I can also be used in combination with steroid therapy or other ITP medications. Only physicians experienced in immunosuppressive therapy and hematology should prescribe this drug.

The medication received favorable HTA recommendations solely from NICE HTA. However, both CADTH and HAS issued negative recommendations regarding its utilization in ITP. Limitations for the use of Avatrombopag include thrombosis.

2.4.3 Romiplostim

Information on Romiplostim is detailed in the table below[17]

Table 31. Romiplostim Drug Information

SCIENTIFIC NAME Romiplostim	
SFDA Classification	Prescription
SFDA	N/A
US FDA	Yes

EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D69. 3
Drug Class	Thrombopoietin Receptor Agonist
Drug Sub-class	Colony Stimulating Factor; Hematopoietic Agent; Thrombopoietic Agent
ATC Code	B02BX04
Pharmacological Class (ASHP)	N/A
DRUG INFORMATION	
Dosage Form	Powder and solvent for solution for injection
Route of Administration	SC use
Dose (Adult) [DDD]	As per the Saudi panel 2019 recommendation, it I recommended as 1-10 mcg/kg subcutaneously once a week, continuous therapy[6]. Note: Use the lowest dose sufficient to maintain platelet count ≥50,000/mm3 as necessary to reduce the risk of bleeding. Do not use to normalize platelet counts. SubQ: Initial: 1 mcg/kg once weekly (based on actual body weight); adjust dose by 1 mcg/kg/week increments to achieve platelet count ≥50,000/mm3 and to reduce the risk of bleeding; Maximum dose: 10 mcg/kg/week (median dose needed to achieve response in clinical trials: 2 to 3 mcg/kg)[17]. Dosage adjustment recommendations: Adjust dose based on platelet count response[17]:

	○ Platelet count <50,000/mm3: Increase weekly dose by 1 mcg/kg. ○ Platelet count >200,000/mm3 to ≤400,000/mm3 for 2 consecutive weeks: Reduce weekly dose by 1 mcg/kg. ○ Platelet count >400,000/mm3: Withhold dose; assess platelet count weekly; when platelet count <200,000/mm3, resume with the weekly dose reduced by 1 mcg/kg. Discontinue if platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks at the maximum recommended dose of 10 mcg/kg/week.
Maximum Daily Dose Adults	Maximum recommended dose of 10 mcg/kg/week.
Dose (pediatrics)	Note: Use the lowest dose sufficient to maintain platelet count ≥50,000/mm3 as necessary to reduce the risk of bleeding. Do not use to normalize platelet counts. Reassess body weight every 12 weeks. Calculate dose using actual body weight. Children and Adolescents: SubQ: Initial: 1 mcg/kg/dose once weekly; adjust dose by 1 mcg/kg/week increments to achieve platelet count ≥50,000/mm3 and to reduce the risk of bleeding; maximum dose: 10 mcg/kg/week[17]. Dosage adjustment recommendations: Adjust dose based on platelet count response: ○ Platelet count <50,000/mm3: Increase weekly dose by 1 mcg/kg. ○ Platelet count >200,000/mm3 to ≤400,000/mm3 for 2 consecutive

	weeks: Reduce weekly dose by 1 mcg/kg. o Platelet count >400,000/mm3: Withhold dose; assess platelet count weekly; when platelet count <200,000/mm3, resume with the weekly dose reduced by 1 mcg/kg. Discontinue if platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks at the maximum recommended dose of 10 mcg/kg/week.
Maximum Daily Dose Pediatrics	Maximum recommended dose of 10 mcg/kg/week.
Adjustment	**Dosing: Older Adult** Refer to adult dosing. **Dosing: Altered Kidney Function: Adult and Pediatric** There are no dosage adjustments provided in the manufacturer's labeling. **Dosing: Hepatic Impairment: Adult and Pediatric** There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits	QL, MD, ST, CU, PA, PE
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	It can be used in combination with steroid therapy or other ITP medications.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	Only physicians experienced in immunosuppressive therapy and hematology should prescribe this drug.
PA (Prior Authorization):	It is recommended for patients who fail to respond to first-line therapy or relapse after the initial response. it is recommended as 1-10 mcg/kg

	subcutaneously once a week, continuous therapy. Drug dosing regimen is based on the platelet count. Maximum recommended dose of 10 mcg/kg/week. It can also be used in combination with steroid therapy or other ITP medications. Only physicians experienced in immunosuppressive therapy and hematology should prescribe this drug.
QL (Quantity Limit):	Maximum recommended dose of 10 mcg/kg/week.
ST (Step Therapy):	It is recommended for patients who fail to respond to first-line therapy or relapse after the initial response
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	Drug dosing regimen is based on the platelet count.
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**<u>Most common:</u>** >10%: **Dermatologic**: Skin rash (children and adolescents: 15%) **Gastrointestinal**: Abdominal pain (11%), diarrhea (children and adolescents: 20%; adults: ≥5%), upper abdominal pain (children and adolescents: 14%) **Hematologic & oncologic**: Acute myelocytic leukemia (4% to 12%), bruise (children and adolescents: 41%) **Nervous system**: Dizziness (17%), headache (35%), insomnia (16%) **Neuromuscular & skeletal**: Arthralgia (26%), limb pain (13%), myalgia (14%) **Respiratory**: Oropharyngeal pain (children and adolescents: 25%; adults: ≥5%), upper respiratory tract infection (children and adolescents: 31%; adults: ≥5%)

	Miscellaneous: Fever (children and adolescents: 24%)
Drug Interactions	**No reported Category X interactions.**
Special Population	N/A
Pregnancy	Based on data from animal reproduction studies, romiplostim may cause fetal harm if administered to a pregnant patient. Outcome data following maternal use of romiplostim during pregnancy are available. Thrombopoietin (TPO) receptor agonists are not currently a preferred treatment of immune thrombocytopenia during pregnancy; use may be considered in very serious cases when other therapies have failed. If a TPO receptor agonist is needed, use of romiplostim may be considered in the third trimester near delivery.
Lactation	It is not known if romiplostim is present in breast milk. Infant outcome data following maternal use of romiplostim while breastfeeding is limited. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer during romiplostim treatment.
Contraindications	There are no contraindications listed in the manufacturer's US labeling. Canadian labeling: Hypersensitivity to romiplostim or any component of the formulation; known history of sensitivity or allergy to any E. coli-derived product.
Monitoring Requirements	Immune thrombocytopenia: CBC with differential and platelets at baseline, weekly during dosage adjustment

	phase of treatment, then monthly, and weekly for at least 2 weeks following discontinuation or completion of treatment. Evaluate for neutralizing antibodies in patients with inadequate response (blood samples may be submitted to the manufacturer for assay
Precautions	**Concerns related to adverse effects:** **Bone marrow reticulin:** May increase the risk for bone marrow reticulin fiber formation; this formation may improve upon discontinuation of therapy. **Concomitant ITP medications:** May be used in combination with other therapies for ITP, including corticosteroids, danazol, azathioprine, immune globulin, or Rho(D) immune globulin. Reduce dose of or discontinue ITP medications when platelet count ≥50,000/mm3. **Error prevention:** To prevent overdose or underdose, use caution when calculating dose and appropriate volume for administration (volume may be very small; administer with syringe that allows for 0.01 mL graduations). **Hyporesponsiveness:** Lack of response or failure to maintain platelet response should trigger investigation into causative factors, including neutralizing antibodies to romiplostim. **Malignancy:** Progression from existing myelodysplastic syndrome (MDS) to acute myeloid leukemia (AML) has been

	observed in clinical trials studying romiplostim for severe thrombocytopenia associated with MDS (not an approved indication); a higher percentage of patients receiving romiplostim experienced transformation to AML (compared to placebo). An increase in the percentage of circulating myeloblasts in peripheral blood counts was also noted (both in patients who progressed to AML and in those who did not); blast cells decreased to baseline after discontinuation in some patients. **Thromboembolism:** Thromboembolism or thrombotic complications with romiplostim therapy may occur from increased platelet counts secondary to drug-induced thrombocytosis, regardless of the underlying disease. Follow dosage adjustment recommendations to minimize the risk for thrombotic or thromboembolic complications. Portal vein thrombosis has been observed in patients with chronic liver disease receiving romiplostim.
Black Box Warning	N/A
REMS	Restricted access to Nplate was previously a REMS requirement via the Nplate NEXUS (Network of Experts Understanding and Supporting Nplate and Patients) program. Patients, prescribers, and pharmacies were required to be enrolled in this program. However, the FDA eliminated this REMS requirement in December 2011. There is currently no restricted access to obtaining Nplate.

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Immune Thrombocytopenic Purpura (ITP) 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 Romiplastim.**

Table 32. Romiplastim HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Romiplastim	NICE[25]	**26 October 2018** **Positive recommendation with restriction** Romiplostim is recommended as an option for treating chronic immune thrombocytopenia in adults, only if: o Their condition is refractory to standard active treatments and rescue therapies or o They have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies. Romiplostim is recommended only if the company makes it available with the discount agreed in the patient access scheme.
	CADTH[26]	**May 27, 2010** **Negative recommendation** The Canadian Expert Drug Advisory Committee (CEDAC) recommends that romiplostim not be listed. Reason for the Recommendation: The Committee considered that romiplostim was not cost-effective and that the harms associated with romiplostim are uncertain.
	HAS[27]	**05 February 2020** **Positive recommendation**

		Favorable opinion for reimbursement in children aged one year and over with chronic (idiopathic) autoimmune thrombocytopenic purpura (ITP), refractory to other treatments (e.g. corticosteroids, immunoglobulins).
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Romiplastim

It is recommended for patients who fail to respond to first-line therapy or relapse after the initial response. It is recommended as 1-10 mcg/kg subcutaneously once a week, continuous therapy. Drug dosing regimen is based on the platelet count. Maximum recommended dose of 10 mcg/kg/week. It can also be used in combination with steroid therapy or other ITP medications. Only physicians experienced in immunosuppressive therapy and hematology should prescribe this drug.

The medication received favorable HTA recommendations from NICE and HAS. However, CADTH issued negative recommendations regarding its utilization in ITP. Limitations for the use of Romiplostim include thrombosis, bone marrow reticulin, concomitant ITP medications and the need to decrease their doses, risk of errors in dosing calculation, hyporesponsiveness, and malignancy.

2.5 Antineoplastic Agents

2.5.1 Cyclophosphamide

Information on Cyclophosphamide is detailed in the table below[17]

Table 33. Cyclophosphamide Drug Information

SCIENTIFIC NAME CYCLOPHOSPHAMIDE	
SFDA Classification	Prescription
SFDA	No
US FDA	No
EMA	No
MHRA	No
PMDA	No
Indication (ICD-10)	D69. 3

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]	300-1000 mg/m2, 2-4 weekly for up to 4 doses; maintenance dose 1-2 mg/kg daily as recommended by the Saudi 2019 Panel [6]
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. CrCl <10 mL/minute: Administer 50%, 75%, or 100% of PO normal dose. IV: Shorter, low-dose regimen (500 mg IV once every 2 weeks for 6 doses): No dosage adjustment necessary. IV: Longer, high-dose regimen (500 to 1,000 mg/m2 IV pulses): CrCl <30 mL/minute: Reduce initial dose to 500 mg/m2 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.

	Peritoneal dialysis: Administer 75% of the normal dose. If possible, allow at least 12 hours before next peritoneal dialysis exchange. CRRT: Administer 100% of the normal dose. 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: 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. It can also be given with steroids or other ITP medications.
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):	Maximum dose has not been established; some experts do not exceed 1,000 mg/dose IV. Do not exceed 150 mg/day oral.
ST (Step Therapy):	This drug is recommended as an alternative option for patients who fail to respond to first-line therapy or relapse after the initial response
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.

	Most serious: Bone marrow suppression and infection, Cardiotoxicity, Hemorrhagic cystitis, Hepatotoxicity, Pulmonary toxicity, Second primary malignancy
Drug Interactions*	**Category X:** • Abrocitinib • Adenovirus (Types 4, 7) Vaccine Depends on International labeling • Baricitinib • BCG (Intravesical) (Immunization) • Brivudine [INT] • Cholera Vaccine Depends on International labeling • Cladribine • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Dipyrone • Ebola Zaire Vaccine (Live) Depends on International labeling • Etanercept • Fexinidazole • Filgotinib • Influenza Virus Vaccine (Live/Attenuated) Depends on International labeling • Japanese Encephalitis Virus Vaccine (Live/Attenuated) Depends on International labeling • Measles, Mumps, and Rubella Virus Vaccine • Measles, Mumps, Rubella, and Varicella Virus Vaccine • Mumps Virus Vaccine Depends on International labeling • Mumps Virus Vaccine

	• Nadofaragene Firadenovec • Natalizumab • Pimecrolimus • Poliovirus Vaccine (Live/Bivalent/Oral) Depends on International labeling • Poliovirus Vaccine (Live/Trivalent/Oral) • Rotavirus Vaccine Depends on International labeling • Ruxolitinib (Topical) • Smallpox Vaccine Live Depends on International labeling • Tacrolimus (Topical) • Talimogene Laherparepvec • Tertomotide • Tofacitinib • Typhoid Vaccine • Upadacitinib • Varicella Virus Vaccine • Voclosporin • Yellow Fever Vaccine • Zoster Vaccine (Live/Attenuated) Depends on International labeling.
Special Population	Dosing adjustment for toxicity: Infants, Children, and Adolescents: Hematologic toxicity: May require dose reduction or treatment interruption. Hemorrhagic cystitis, severe: Discontinue treatment. Older Adult Considerations 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 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. 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.

	Hypersensitivity: Possible cross-sensitivity with other alkylating agents may occur. 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 Immune Thrombocytopenic Purpura (ITP) 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 34. 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 for patients who fail to respond to first-line therapy or relapse after the initial response. Only physicians experienced in immunosuppressive therapy and hematology should prescribe Cyclophosphamide. Cyclophosphamide 300-1000 mg/m2, 2-4 weekly for up to 4 doses; maintenance dose 1-2 mg/kg daily. Maximum dose has not been established; some experts do not exceed 1,000 mg/dose IV. Do not exceed 150 mg/day oral. Antiemetics are recommended in combination with cyclophosphamide. This drug can also be used in combination with steroids, or other ITP medications. There are no HTA recommendations regarding its use in ITP. Limitations for the use of

Cyclophosphamide include bone marrow suppression, cardiotoxicity, and hepatotoxicity.

2.5.2 Vincristine

The table below showcases the drug information related to Vincristine[17]:

Table 35. Vincristine Drug Information

Scientific Name Vincristine	
SFDA Classification	Prescription
SFDA approved Indication	Yes, Patients with true ITP refractory to splenectomy and short-term treatment with adrenocortical steroids may respond to vincristine but the medicinal product is not recommended as primary treatment of this disorder. Recommended weekly doses of vincristine given for 3 to 4 weeks have produced permanent remissions in some patients. If patients fail to respond after 3 to 6 doses, it is unlikely that there will be any beneficial results with additional doses.
FDA approved	No
EMA approved	No
MHRA approved	Yes
PMDA approved	Yes, Off label
Indication (ICD-10)	D69. 3
Drug Class	Antineoplastic agent
Drug Sub-class	Antimicrotubular, Vinca Alkaloid
ATC Code	L01CA02
Pharmacological Class (ASHP)	Antineoplastic Agents
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Intravenous
Dose (Adult) [DDD]	1-2 mg weekly for up to 3-4 doses as recommended by the Saudi Panel 2019[6]
Dose (Pediatrics)	N/A

Adjustment	Hepatic Impairment (Adult/Pediatric): - 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 steroids or other ITP therapy
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 for patients who fail to respond to first-line therapy or relapse after the initial response
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
Maximum Daily Dose Adults	2 mg
Maximum Daily Dose Pediatrics	2 mg
SAFETY	
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 - Most serious: Ataxia, paralysis, acute respiratory distress syndrome, uric acid nephropathy

Drug Interactions*	- Risk X: Fexinidazole, Fusidic Acid (Systemic) - 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) - Hepatic function tests - CBC with differential, serum uric acid. - 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. - Monitor infusion site. - Perform neurologic examination, monitor for constipation/ileus and for signs/symptoms of peripheral neuropathy.
Precautions	- Extravasation - Gastrointestinal toxicity - Neurotoxicity - Respiratory effects - Uric acid nephropathy - Hepatic impairment: Use with caution

	- **For IV administration only; fatal if given by other routes**
Black Box Warning	- Experienced physician - Extravasation - Appropriate administration
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Immune Thrombocytopenic Purpura (ITP) 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 36. Vincristine HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Vincristine	NICE	N/A
	CADTH	N/A
	HAS[12]	**February 16, 2006** The actual benefit of Vincristine 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 patients who fail to respond to first-line therapy or relapse after the initial response. This drug is given as 1-2 mg weekly for up to 3-4 doses. It can be used in combination with steroid therapy or other ITP medications.
Only physicians experienced in oncology and hematology should prescribe Vincristine. There are no HTA recommendations regarding the use of Vincristine in ITP except for 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.

2.5.3 Vinblastine

The table below showcases the drug information related to Vinblastine[17]:

Table 37. Vinblastine Drug Information

Scientific Name Vinblastine	
SFDA Classification	Prescription
SFDA approved Indication	No
FDA approved	No
EMA approved	No
MHRA approved	No
PMDA approved	No
Indication (ICD-10)	D69. 3
Drug Class	Antineoplastic agent
Drug Sub-class	Vinca Alkaloid
ATC Code	L01CA01
Pharmacological Class (ASHP)	Antineoplastic Agents
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Intravenous use
Dose (Adult) [DDD]	6 mg/m2, weekly for 3-4 doses
Dose (Pediatrics)	N/A
Adjustment	**Altered Kidney Function: Adult** No dosage adjustment necessary. **Dosing: Hepatic Impairment: Adult** Toxicity may be increased in patients with hepatic dysfunction. The manufacturer's labeling recommends the following adjustment: Serum bilirubin >3 mg/dL: Administer 50% of dose. The following adjustments have also been recommended:

	Serum bilirubin 1.5 to 3 mg/dL or transaminases 2 to 3 times ULN: Administer 50% of dose. Serum bilirubin >3 times ULN: Avoid use. **Dosing: Obesity: Adult** American Society of Clinical Oncology guidelines for appropriate systemic therapy dosing in adults with cancer with a BMI ≥30 kg/m2: Utilize patient's actual body weight for calculation of BSA- or weight-based dosing; manage regimen-related toxicities in the same manner as for patients with a BMI <30 kg/m2; if a dose reduction is utilized due to toxicity, may consider resumption of full weight-based dosing (or previously tolerated dose level) with subsequent cycles only if dose escalations are allowed in the prescribing information, if contributing underlying factors (eg, hepatic or kidney impairment) are sufficiently resolved, AND if performance status has markedly improved or is considered adequate
Prescribing edits	MD, ST, QL, CU
AGE (Age Edit)	N/A
CU (Concurrent Use)	Can be used in combination with steroids or other ITP medications
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by a hematologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum 10 mg total dose/injection
ST (Step Therapy)	This drug is recommended for patients who fail to respond to first-line therapy or relapse after the initial response
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A

Maximum Daily Dose Adults	Maximum 10 mg total dose/injection
Maximum Daily Dose Pediatrics	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Frequency not defined.** Cardiovascular: Angina pectoris, cerebrovascular accident, ECG abnormality, hypertension (common), ischemic heart disease, limb ischemia, myocardial infarction, Raynaud's phenomenon Central nervous system: Decreased deep tendon reflex, depression, dizziness, headache, malaise (common), metallic taste, neurotoxicity (duration: >24 hours), paresthesia, peripheral neuritis, seizure, tumor pain (common), vertigo. Dermatologic: Alopecia (common), dermatitis, skin blister, skin photosensitivity (rare), skin rash Endocrine & metabolic: Hyperuricemia, SIADH (syndrome of inappropriate antidiuretic hormone secretion) Gastrointestinal: Abdominal pain, anorexia, constipation (common), diarrhea, enterocolitis (hemorrhagic), gastrointestinal hemorrhage, intestinal obstruction, nausea (mild), paralytic ileus, stomatitis, toxic megacolon, vomiting (mild) Genitourinary: Azoospermia, urinary retention

	Hematologic & oncologic: Anemia, bone marrow depression (common), granulocytopenia (common; nadir: 5 to 10 days; recovery: 7 to 14 days; dose-limiting toxicity), hemolytic uremic syndrome, leukopenia (common; nadir: 5 to 10 days; recovery: 7 to 14 days; dose-limiting toxicity), rectal hemorrhage, thrombocytopenia (recovery within a few days), thrombotic thrombocytopenic purpura Local: Local irritation Neuromuscular & skeletal: Jaw pain (common), myalgia, ostealgia (common), weakness Ophthalmic: Nystagmus Otic: Auditory disturbance, deafness, vestibular disturbance Respiratory: Bronchospasm, dyspnea, pharyngitis Miscellaneous: Radiation recall phenomenon
Drug Interactions	**CATEGORY X interactions:** - Abrocitinib - Baricitinib - BCG (Intravesical) - Brivudine - Chikungunya Vaccine (Live) - Chloramphenicol (Systemic) - Cladribine - Dengue Tetravalent Vaccine (Live) - Deucravacitinib - Dipyrone - Etrasimod

	- Fexinidazole - Filgotinib - Fusidic Acid (Systemic) - Mumps- Rubella- or Varicella-Containing Live Vaccines - Nadofaragene Firadenovec - Natalizumab - Pimecrolimus - Poliovirus Vaccine (Live/Trivalent/Oral) - Ritlecitinib - Ruxolitinib (Topical) - Tacrolimus (Topical) - Talimogene Laherparepvec - Tertomotide - Tofacitinib - Typhoid Vaccine - Upadacitinib - Vaccines (Live) - Yellow fever vaccine
Special Population	N/A
Pregnancy	Patients who could become pregnant should avoid becoming pregnant during vinblastine treatment. Reversible amenorrhea may occur when vinblastine is used in some combination regimens (dose related). Aspermia has been reported in males who have received treatment with vinblastine. Based on placental perfusion studies, vinblastine is expected to cross the placenta. Outcome information following maternal use of vinblastine as a single agent or as part of combination therapy during pregnancy is available
Lactation	It is not known if vinblastine is present in breast milk.

	Samples from a lactating patient treated with the ABVD regimen for Hodgkin lymphoma demonstrated changes in the bacterial and metabolic composition of breast milk when compared to untreated healthy patients (Urbaniak 2014). Patients using this regimen during pregnancy may have difficulty initiating breastfeeding postpartum (Stopenski 2017). Due to the potential for serious adverse reactions in the breastfed infant, a decision should be made to discontinue vinblastine or to discontinue breastfeeding, taking into account the importance of treatment to the mother.
Contraindications	Significant granulocytopenia (unless as a result of condition being treated); presence of bacterial infection. Canadian labeling: Additional contraindications not in the US labeling: Pregnancy
Monitoring Requirements	
Precautions	**Concerns related to adverse effects:** **Bone marrow suppression**: Leukopenia commonly occurs; granulocytopenia may be severe with higher doses. The leukocyte nadir generally occurs 5 to 10 days after administration; recovery typically occurs 7 to 14 days later. Leukopenia may be more pronounced in cachectic patients and patients with skin ulceration and may be less pronounced with lower doses used for maintenance therapy. Leukocytes and platelets may fall considerably with moderate doses when marrow is infiltrated with malignant cells (further use in this situation is not

	recommended). Thrombocytopenia and anemia may occur rarely. **Extravasation**: Vinblastine is a vesicant; ensure proper needle or catheter placement prior to and during infusion. Avoid extravasation. Extravasation may cause significant irritation. Individuals administering should be experienced in vinblastine administration. **Gastrointestinal toxicity**: Stomatitis may occur (rare); may be disabling, but is usually reversible. **Neurotoxicity**: May rarely cause disabling neurotoxicity; usually reversible. Seizures and severe and permanent CNS damage have occurred with higher than recommended doses and/or when administered more frequently than recommended. **Pulmonary toxicity**: Acute shortness of breath and severe bronchospasm have been reported, most often in association with concurrent administration of mitomycin; may occur within minutes to several hours following vinblastine administration or up to 14 days following mitomycin administration; use caution in patients with preexisting pulmonary disease. **Disease-related concerns:** **Ischemic heart disease**: Use with caution in patients with ischemic heart disease. **Dosage form specific issues:**

	Benzyl alcohol and derivatives: Some dosage forms may contain benzyl alcohol; large amounts of benzyl alcohol (≥99 mg/kg/day) have been associated with a potentially fatal toxicity ("gasping syndrome") in neonates; the "gasping syndrome" consists of metabolic acidosis, respiratory distress, gasping respirations, CNS dysfunction (including convulsions, intracranial hemorrhage), hypotension, and cardiovascular collapse; some data suggests that benzoate displaces bilirubin from protein binding sites; avoid or use dosage forms containing benzyl alcohol with caution in neonates. See manufacturer's labeling. **Other warnings/precautions:** **NOT for intrathecal use**: For IV use only. Administration by other routes may result in death. To prevent administration errors, the Institute for Safe Medication Practices (ISMP) Targeted Medication Safety Best Practices for Hospitals initiative strongly recommends dispensing vinblastine diluted in a minibag. Vinblastine should NOT be prepared during the preparation of any medications intended for CNS administration. After preparation, keep vinblastine in a location away from the separate storage location recommended for medications intended for CNS administration. Vinblastine should NOT be delivered to the patient at the same time with any medications intended for CNS administration.
Black Box Warning	**Experienced physician:**

	This preparation should be administered by individuals experienced in the administration of vinblastine sulfate. **Extravasation:** It is extremely important that the intravenous needle or catheter be properly positioned before any vinblastine sulfate is injected. Leakage into surrounding tissue during intravenous administration of vinblastine may cause considerable irritation. If extravasation occurs, the injection should be discontinued immediately, and any remaining portion of the dose should then be introduced into another vein. Local injection of hyaluronidase and the application of moderate heat to the area of leakage help disperse the drug and are thought to minimize discomfort and the possibility of cellulitis. **Appropriate administration:** For intravenous use only - fatal if given by other routes.
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Immune Thrombocytopenic Purpura (ITP) 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 Vinblastine.**

Table 38. Vinblastine HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Vinblastine	NICE	N/A
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Vinblastine

This drug is recommended as an alternative option for patients who fail to respond to first-line therapy or relapse after the initial response. This drug is given as 6 mg/m2 (maximum 10 mg total dose/injection), weekly for 3-4 doses. It can be used in combination with steroids or other ITP therapy.
Only physicians experienced in oncology and hematology should prescribe Vinblastine. There are no HTA recommendations regarding the use of Vinblastine in ITP. Limitations for the use of Vinblastine include neurotoxicity, bone marrow suppression, extravasation, GI toxicity, respiratory effects, its caution use in ischemic disease patients and the need to have an experienced personnel to administer this drug intravenously only.

2.6 Androgenic Hormones

2.6.1 Danazol

Information on Danazol is detailed in the table below[17]

Table 39. Danazol Drug Information

SCIENTIFIC NAME Danazol	
SFDA Classification	Prescription
SFDA	No
US FDA	No
EMA	No
MHRA	No
PMDA	No
Indication (ICD-10)	D69. 3
Drug Class	Androgen

Drug Sub-class	Androgen hormone
ATC Code	G03XA01
Pharmacological Class (ASHP)	N/A
DRUG INFORMATION	
Dosage Form	Capsule
Route of Administration	Oral use
Dose (Adult) [DDD]	100-800 mg orally daily in divided doses, as per the Saudi panel 2019 recommendations[6]. Immune thrombocytopenia, refractory (off-label use)[17]: Note: May be considered in patients whose symptoms are refractory to or who are unable to take other preferred agents. Oral: 200 mg 2 to 4 times/day; approximate time to response is 3 to 6 months or 600 mg once daily for at least 6 months followed by 400 mg once daily for 3 months, then (if remission maintained) 200 mg once daily
Maximum Daily Dose Adults	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics	N/A
Adjustment	**Dosing: Older Adult** Refer to adult dosing. **Dosing: Altered Kidney Function: Adult** There are no dosage adjustments provided in the manufacturer's labeling. Use is contraindicated in patients with markedly impaired renal function. **Dosing: Hepatic Impairment: Adult** There are no dosage adjustments provided in the manufacturer's labeling.

	Use is contraindicated in patients with markedly impaired hepatic function.
Prescribing edits	MD, ST, CU, AGE
AGE (Age Edit):	Not studied in the pediatric population for management of refractory ITP
CU (Concurrent Use Edit):	Can be used in combination with steroids or other ITP medications.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	Only physicians experienced in immunosuppressive therapy and hematology should prescribe this drug.
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	It is recommended for patients who fail to respond to first-line therapy or relapse after the initial response.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** **Post-marketing:** **Cardiovascular:** Acute myocardial infarction, edema, flushing, increased blood pressure, palpitations, syncope, tachycardia, thrombosis (including thromboembolic complications and thromboembolism [cerebrovascular accident, sagittal sinus thrombosis]) **Dermatologic:** Acne vulgaris, alopecia, diaphoresis, erythema multiforme, maculopapular rash, papular rash, pruritus, purpuric rash, seborrhea, skin photosensitivity, Stevens-Johnson syndrome, urticaria, vesicular eruption **Endocrine & metabolic:** Altered serum glucose (including abnormal glucose tolerance test), change in libido, changes in serum lipids (including decreased HDL cholesterol and

	increased LDL cholesterol), decreased sex hormone binding globulin, decreased thyroxine binding globulin, exacerbation of porphyria, fluid retention, hirsutism, increased sex hormone-binding globulin, increased thyroxine binding globulin, menstrual disease (amenorrhea, irregular menses, spotty menstruation), weight gain. **Gastrointestinal:** Change in appetite, constipation, gastroenteritis, gingival hemorrhage, nausea, pancreatitis, vomiting **Genitourinary:** Breast atrophy, clitoromegaly, decreased ejaculate volume, hematuria, inhibition of spermatogenesis, nipple discharge, pelvic pain, spermatozoa disorder (including changes in asthenospermia, semen viscosity, and sperm count), vaginal dryness, vaginal irritation **Hematologic & oncologic:** Abnormal erythrocytes (increased), change in serum protein, eosinophilia, leukocytosis, leukopenia, petechial rash, polycythemia, purpuric disease (splenic peliosis), thrombocythemia, thrombocytopenia. **Hepatic:** Hepatic adenoma, hepatic failure, hepatic neoplasm (malignant; after prolonged use; hepatocellular neoplasm), hepatotoxicity (idiosyncratic), increased liver enzymes, jaundice (including cholestatic jaundice and hepatocellular jaundice), peliosis hepatitis **Nervous system:** Anxiety, asthenia, chills, depression, dizziness, emotional lability, fatigue, Guillain-Barre syndrome, headache, intracranial hypertension, nervousness, paresthesia, seizure, sleep

	disorder, voice disorder (deepening of the voice, hoarseness, instability, sore throat), tremor **Neuromuscular & skeletal:** Arthralgia, back pain, increased creatine phosphokinase in blood specimen, joint swelling, limb pain, muscle cramps, muscle spasm, myalgia, neck pain **Ophthalmic:** Cataract, visual disturbance **Respiratory:** Interstitial pneumonitis, nasal congestion **Miscellaneous:** Fever
Drug Interactions	**Category X:** • Pimozide • Simvastatin
Special Population	N/A
Pregnancy	Evaluate pregnancy status prior to use in patients who may become pregnant. A sensitive test capable of determining early pregnancy is recommended immediately prior to start of therapy (eg, beta subunit test, if available). A nonhormonal method of contraception should be used during therapy. Menstrual disturbances may occur during therapy. Although ovulation may return within 60 to 90 days once danazol is discontinued, persistent amenorrhea may occur. Spermatogenesis and abnormalities in semen volume, viscosity, count, and motility may occur with long-term therapy. Androgens cross the placenta. Exposure to danazol in utero may result in androgenic effects on the female fetus; reports of clitoral hypertrophy, labial

	fusion, urogenital sinus defect, vaginal atresia, and ambiguous genitalia have been received. Use of danazol in pregnancy is contraindicated. If a patient becomes pregnant while taking danazol, administration of the drug should be discontinued, and the patient should be apprised of the potential risk to the fetus.
Lactation	Use of danazol is contraindicated in breastfeeding patients.
Contraindications	Hypersensitivity to danazol or any component of the formulation; undiagnosed abnormal genital bleeding; pregnancy; breastfeeding; porphyria; markedly impaired hepatic, renal, or cardiac function; androgen-dependent tumor; active or history of thrombosis or thromboembolic disease *Canadian labeling:* Additional contraindications (not in the US labeling): Genital neoplasia; concomitant administration with simvastatin.
Monitoring Requirements	Liver and renal function tests (periodically); hematologic parameters; lipid panel. Signs and symptoms of intracranial hypertension (papilledema, headache, nausea, vomiting), androgenic changes, and/or fluid retention. Evaluate pregnancy status prior to use in patients who may become pregnant.
Precautions	**Concerns related to adverse effects:** **Androgenic effects:** May cause nonreversible androgenic effects.

	Blood lipid changes: Anabolic steroids may cause blood lipid changes (decreased high density lipoproteins and increased low density lipoproteins) with increased risk of arteriosclerosis and coronary artery disease. **Disease-related concerns:** **Cyclic breast pain (mastalgia) associated with benign breast disorders:** Use is reserved for severe and refractory cases that have not responded to conservative measures and analgesics. Malignancy should be ruled out prior to therapy. **Diabetes:** Use with caution in patients with diabetes mellitus; insulin requirements may be increased; monitor carefully. **Edematous conditions:** Use with caution in patients with conditions influenced by edema (eg, cardiovascular disease, migraine, seizure disorder, renal impairment); danazol may cause fluid retention. **Porphyria:** May cause exacerbations of acute intermittent porphyria; use is contraindicated in patients with porphyria. **Other warnings/precautions:** **Appropriate use:** Endometriosis: Danazol is generally reserved for the treatment of pain associated with endometriosis when other agents are not available, due to its high incidence of adverse events
Black Box Warning	Thromboembolic events

	Pregnancy Hepatic effects Intracranial hypertension
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Immune Thrombocytopenic Purpura (ITP) 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 Danazol.**

Table 40. Danazol HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Danazol	NICE	N/A
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Danazol

The drug is not studied in the pediatric population for management of refractory ITP. Can be used in combination with steroids or other ITP medications. Only physicians experienced in immunosuppressive therapy and hematology should prescribe this drug. It is recommended for patients who fail to respond to first-line therapy or relapse after the initial response.

There are no HTA recommendations regarding its use in ITP. Limitations for the use of Danazol include thrombosis, hepatic effects, intracranial hypertension, and its contraindication in pregnancy.

Section 3.0 Key Recommendations Synthesis

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

- The first-line treatment is similar in most cases of primary and secondary ITP, namely, glucocorticoids and/or IVIg. when choosing the second-line option, one has to consider seriously the underlying disease when managing secondary ITP [7].
- The choice of treatment should be individualized, involving a discussion with the patient, consideration of the severity of the bleeding episodes, comorbidities, the toxicity profile of each therapy option, drug availability, anticipated surgical procedures, the cost of therapy, and patient age, lifestyle, and quality of life. [6]
- Most patients with no or minimal bleeding (limited to skin manifestations only) may be observed, provided that their platelet count continues to be >20–30 × 10^9 /L. [6 8]
- Inpatient management is suggested for patients with newly diagnosed ITP who have a platelet count below 20 × 109/L and are asymptomatic or have minor symptoms [9].
- For patients with a platelet count at the lower end of this threshold, those with additional comorbidities, anticoagulant or antiplatelet agents, or need to follow the procedures. Corticosteroid treatment may be appropriate for elderly patients (aged >60 yr) [10].
- First-line medications include corticosteroids, intravenous immunoglobulin (IvIg), or anti-D immunoglobulin (anti-D) [6].
    - IVIG is useful in the emergency settings (ongoing bleeding, surgery)
    - Use of Anti-D is limited to Rh +ve patients who have an acceptable hemoglobin level and a functional spleen.
- Patients, who fail to exhibit significant response with first-line therapy or relapse after the initial response, require second-line therapy [6].
- Not all second-line options are similar. Therefore, factors including comorbidities, age, and patient preference play a major role in the choice of therapy [6].
- Options include: Rituximab, TPO-RA (Thrombopoietin receptor agonists), Mycophenolate mofetil, Danazol, Dapsone, Azathioprine, Cyclosporine A, Cyclophosphamide, and Vinca alkaloids. [6]

- In patients who fail second-line therapies or in cases of bleeding emergency that is life-threatening, splenectomy will continue to be an important option [6].
- Combined therapies are usually more effective than monotherapy in refractory patients. Ideally, agents with different mechanisms of action should be combined. Rescues have been described using steroids concomitantly with rituximab or TPO-RA [7].
- In the event of no response to one treatment, adding a new therapy concomitantly may be better than suspending the former and starting with the new one only [7].
- Fostamatinib was approved for the treatment of chronic ITP in adults in 2018 [6].
- Duration of therapy: Recommends in favor of short course (≤ 6 weeks) and against longer course of prednisone (> 6 weeks including taper). Treatment should not last more than three cycles in the case of dexamethasone [9 7 10].
- In life-threatening bleeding, the guidelines recommend platelet transfusions to achieve hemostasis, along with IVIg (1–2 g/kg), and steroids (methylprednisolone up to 1000 mg intravenous daily for 1–5 days or high dose dexamethasone 40 mg daily intravenous or orally for 4 days) [8].
- Vinka alkaloids can be considered for rare cases of refractory or multiply relapsed disease and life-threatening bleeding [8].
- In pediatric patients [7]:
    - First line options include prednisone, methylprednisolone, and high dose IVIG.
    - Second options in persistent ITP include IV Anti-D Ig (if Rh+) + steroids combination
    - In chronic ITP, TPO-RA long term is recommended
    - Third line options include Mycophenolate mofetil, Rituximab, and dapsone
- In elderly patients [7]:
    - When there is severe bleeding, hospitalization and immediate instauration of treatment is recommended.
    - First-line options – in the presence of severe bleeding or without: IVIG with corticosteroids combination.
    - Additional options when rapid increases in platelet counts are required: TPO-RA and Vinca alkaloids

- In pregnant patients [7]:
    - First line options include prednisone or IVIG when prednisone-induced side effects, severe bleeding or requirement of rapid recovery of platelets to prepare for deliver.
    - Other options include Azathioprine, cyclosporin. If splenectomy is decided (data regarding safety/efficacy are limited, risk of neonatal Thrombocytopenia), the procedure should be performed in the second trimester
    - Management of neonates will depend on their platelet count values

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of Immune 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
((((((((((((((((((((((((((((Purpura, Thrombocytopenic, Idiopathic[MeSH Terms]) OR (Idiopathic Thrombocytopenic Purpura[Title/Abstract])) OR (Idiopathic Thrombocytopenic Purpuras[Title/Abstract])) OR (Purpura, Idiopathic Thrombocytopenic[Title/Abstract])) OR (Purpuras, Idiopathic Thrombocytopenic[Title/Abstract])) OR (Thrombocytopenic Purpura, Idiopathic[Title/Abstract])) OR (Thrombocytopenic Purpuras, Idiopathic[Title/Abstract])) OR (Immune Thrombocytopenic Purpura[Title/Abstract])) OR (Immune Thrombocytopenic Purpuras[Title/Abstract])) OR (Purpura, Immune Thrombocytopenic[Title/Abstract])) OR (Purpuras, Immune Thrombocytopenic[Title/Abstract])) OR (Thrombocytopenic Purpura, Immune[Title/Abstract])) OR (Thrombocytopenic Purpuras, Immune[Title/Abstract])) OR (Immune Thrombocytopenia[Title/Abstract])) OR (Immune Thrombocytopenias[Title/Abstract])) OR (Thrombocytopenia, Immune[Title/Abstract])) OR (Thrombocytopenias, Immune[Title/Abstract])) OR (Thrombocytopenic Purpura, Autoimmune[Title/Abstract])) OR (Werlhof Disease[Title/Abstract])) OR (Disease, Werlhof[Title/Abstract])) OR (Werlhof's Disease[Title/Abstract])) OR (Disease, Werlhof's[Title/Abstract])) OR	Meta-Analysis, Systematic Review, in the last 5 years	("purpura, thrombocytopenic, idiopathic"[MeSH Terms] OR "idiopathic thrombocytopenic purpura"[Title/Abstract] OR "idiopathic thrombocytopenic purpuras"[Title/Abstract] OR "purpura idiopathic thrombocytopenic"[Title/Abstract] OR (("Purpura"[MeSH Terms] OR "Purpura"[All Fields] OR "Purpuras"[All Fields]) AND "idiopathic thrombocytopenic"[Title/Abstract]) OR "thrombocytopenic purpura idiopathic"[Title/Abstract] OR (("purpura, thrombocytopenic"[MeSH Terms] OR ("Purpura"[All Fields] AND "Thrombocytopenic"[All Fields]) OR "thrombocytopenic purpura"[All Fields] OR ("Thrombocytopenic"[All Fields] AND "Purpuras"[All Fields]) OR "thrombocytopenic purpuras"[All Fields]) AND "Idiopathic"[Title/Abstract]) OR "immune thrombocytopenic purpura"[Title/Abstract] OR (("Immune"[All Fields] OR "immuned"[All Fields] OR "immunes"[All Fields] OR "immunization"[All Fields] OR "vaccination"[MeSH Terms] OR "vaccination"[All Fields] OR "immunization"[All Fields] OR "immunization"[MeSH Terms] OR "immunisations"[All Fields] OR "immunizations"[All Fields] OR "immunise"[All Fields] OR "immunised"[All Fields] OR "immuniser"[All Fields] OR "immunisers"[All Fields] OR "immunising"[All Fields] OR "immunities"[All Fields] OR	42,071

(Werlhofs Disease[Title/Abstract])) OR (Autoimmune Thrombocytopenia[Title/Abstract])) OR (Autoimmune Thrombocytopenias[Title/Abstract])) OR (Thrombocytopenia, Autoimmune[Title/Abstract])) OR (Thrombocytopenias, Autoimmune[Title/Abstract])) OR (Autoimmune Thrombocytopenic Purpura[Title/Abstract])) OR (Autoimmune Thrombocytopenic Purpuras[Title/Abstract])) OR (Purpura, Autoimmune Thrombocytopenic[Title/Abstract])) OR (Purpuras, Autoimmune Thrombocytopenic[Title/Abstract])) OR (Purpura, Thrombocytopenic, Autoimmune[Title/Abstract])		"immunity"[MeSH Terms] OR "immunity"[All Fields] OR "immunization s"[All Fields] OR "immunize"[All Fields] OR "immunized"[All Fields] OR "immunizer"[All Fields] OR "immunizers"[All Fields] OR "immunizes"[All Fields] OR "immunizing"[All Fields]) AND "thrombocytopenic purpuras"[Title/Abstract]) OR "purpura immune thrombocytopenic"[Title/Abstract] OR (("Purpura"[MeSH Terms] OR "Purpura"[All Fields] OR "Purpuras"[All Fields]) AND "immune thrombocytopenic"[Title/Abstract]) OR "thrombocytopenic purpura immune"[Title/Abstract] OR (("purpura, thrombocytopenic"[MeSH Terms] OR ("Purpura"[All Fields] AND "Thrombocytopenic"[All Fields]) OR "thrombocytopenic purpura"[All Fields] OR ("Thrombocytopenic"[All Fields] AND "Purpuras"[All Fields]) OR "thrombocytopenic purpuras"[All Fields]) AND "Immune"[Title/Abstract]) OR "immune thrombocytopenia"[Title/Abstract] OR "immune thrombocytopenias"[Title/Abstract] OR "thrombocytopenia immune"[Title/Abstract] OR "thrombocytopenias immune"[Title/Abstract] OR "thrombocytopenic purpura autoimmune"[Title/Abstract] OR "werlhof disease"[Title/Abstract] OR "disease werlhof"[Title/Abstract] OR "werlhof s disease"[Title/Abstract] OR (("Disease"[MeSH Terms] OR "Disease"[All Fields] OR "diseases"[All Fields] OR "disease s"[All Fields] OR "diseased"[All		

		Fields]) AND "Werlhof's"[Title/Abstract]) OR ("Disease"[Title/Abstract]) OR "autoimmune thrombocytopenia"[Title/Abstract] OR "autoimmune thrombocytopenias"[Title/Abstract] OR "thrombocytopenia autoimmune"[Title/Abstract] OR "thrombocytopenias autoimmune"[Title/Abstract] OR "autoimmune thrombocytopenic purpura"[Title/Abstract] OR (("Autoimmune"[All Fields] OR "autoimmunity"[MeSH Terms] OR "autoimmunity"[All Fields] OR "autoimmunities"[All Fields] OR "autoimmunization"[All Fields] OR "autoimmunizing"[All Fields]) AND "thrombocytopenic purpuras"[Title/Abstract]) OR (("Purpura"[MeSH Terms] OR "Purpura"[All Fields] OR "Purpuras"[All Fields]) AND "autoimmune thrombocytopenic"[Title/Abstract]) OR (("Purpura"[MeSH Terms] OR "Purpura"[All Fields] OR "Purpuras"[All Fields]) AND "autoimmune thrombocytopenic"[Title/Abstract]) OR (("Purpura"[MeSH Terms] OR "Purpura"[All Fields] OR "Purpuras"[All Fields]) AND "thrombocytopenic autoimmune"[Title/Abstract])) AND ((y_5[Filter]) AND (meta-analysis[Filter] OR systematicreview[Filter]))	
((((((((((((((((((((((((((((Purpura, Thrombocytopenic, Idiopathic[MeSH Terms]) OR (Idiopathic Thrombocytopenic Purpura[Title/Abstract])) OR (Idiopathic Thrombocytopenic Purpuras[Title/Abstract])) OR (Purpura, Idiopathic Thrombocytopenic[Title/Abstract]))	Guideline, in the last 5 years	("purpura, thrombocytopenic, idiopathic"[MeSH Terms] OR "idiopathic thrombocytopenic purpura"[Title/Abstract] OR "idiopathic thrombocytopenic purpuras"[Title/Abstract] OR "purpura idiopathic thrombocytopenic"[Title/Abstract] OR (("Purpura"[MeSH Terms] OR	1,647

OR (Purpuras, Idiopathic Thrombocytopenic[Title/Abstract])) OR (Thrombocytopenic Purpura, Idiopathic[Title/Abstract])) OR (Thrombocytopenic Purpuras, Idiopathic[Title/Abstract])) OR (Immune Thrombocytopenic Purpura[Title/Abstract])) OR (Immune Thrombocytopenic Purpuras[Title/Abstract])) OR (Purpura, Immune Thrombocytopenic[Title/Abstract])) OR (Purpuras, Immune Thrombocytopenic[Title/Abstract])) OR (Thrombocytopenic Purpura, Immune[Title/Abstract])) OR (Thrombocytopenic Purpuras, Immune[Title/Abstract])) OR (Immune Thrombocytopenia[Title/Abstract])) OR (Immune Thrombocytopenias[Title/Abstract])) OR (Thrombocytopenia, Immune[Title/Abstract])) OR (Thrombocytopenias, Immune[Title/Abstract])) OR (Thrombocytopenic Purpura, Autoimmune[Title/Abstract])) OR (Werlhof Disease[Title/Abstract])) OR (Disease, Werlhof[Title/Abstract])) OR (Werlhof's Disease[Title/Abstract])) OR (Disease, Werlhof's[Title/Abstract])) OR (Werlhofs Disease[Title/Abstract])) OR (Autoimmune Thrombocytopenia[Title/Abstract])) OR (Autoimmune Thrombocytopenias[Title/Abstract])) OR (Thrombocytopenia, Autoimmune[Title/Abstract])) OR (Thrombocytopenias, Autoimmune[Title/Abstract])) OR (Autoimmune Thrombocytopenic Purpura[Title/Abstract])) OR (Autoimmune Thrombocytopenic Purpuras[Title/Abstract])) OR (Purpura, Autoimmune		"Purpura"[All Fields] OR "Purpuras"[All Fields]) AND "idiopathic thrombocytopenic"[Title/Abstract]) OR "thrombocytopenic purpura idiopathic"[Title/Abstract] OR (("purpura, thrombocytopenic"[MeSH Terms] OR ("Purpura"[All Fields] AND "Thrombocytopenic"[All Fields]) OR "thrombocytopenic purpura"[All Fields] OR ("Thrombocytopenic"[All Fields] AND "Purpuras"[All Fields]) OR "thrombocytopenic purpuras"[All Fields]) AND "Idiopathic"[Title/Abstract]) OR "immune thrombocytopenic purpura"[Title/Abstract] OR (("Immune"[All Fields] OR "immuned"[All Fields] OR "immunes"[All Fields] OR "immunization"[All Fields] OR "vaccination"[MeSH Terms] OR "vaccination"[All Fields] OR "immunization"[All Fields] OR "immunization"[MeSH Terms] OR "immunisations"[All Fields] OR "immunizations"[All Fields] OR "immunise"[All Fields] OR "immunised"[All Fields] OR "immuniser"[All Fields] OR "immunisers"[All Fields] OR "immunising"[All Fields] OR "immunities"[All Fields] OR "immunity"[MeSH Terms] OR "immunity"[All Fields] OR "immunization s"[All Fields] OR "immunize"[All Fields] OR "immunized"[All Fields] OR "immunizer"[All Fields] OR "immunizers"[All Fields] OR "immunizes"[All Fields] OR "immunizing"[All Fields]) AND "thrombocytopenic purpuras"[Title/Abstract]) OR "purpura immune thrombocytopenic"[Title/Abstract] OR (("Purpura"[MeSH Terms] OR	

Thrombocytopenic[Title/Abstract])) OR (Purpuras, Autoimmune Thrombocytopenic[Title/Abstract])) OR (Purpura, Thrombocytopenic, Autoimmune[Title/Abstract])		"Purpura"[All Fields] OR "Purpuras"[All Fields]) AND "immune thrombocytopenic"[Title/Abstract]) OR "thrombocytopenic purpura immune"[Title/Abstract] OR (("purpura, thrombocytopenic"[MeSH Terms] OR ("Purpura"[All Fields] AND "Thrombocytopenic"[All Fields]) OR "thrombocytopenic purpura"[All Fields] OR ("Thrombocytopenic"[All Fields] AND "Purpuras"[All Fields]) OR "thrombocytopenic purpuras"[All Fields]) AND "Immune"[Title/Abstract]) OR "immune thrombocytopenia"[Title/Abstract] OR "immune thrombocytopenias"[Title/Abstract] OR "thrombocytopenia immune"[Title/Abstract] OR "thrombocytopenias immune"[Title/Abstract] OR "thrombocytopenic purpura autoimmune"[Title/Abstract] OR "werlhof disease"[Title/Abstract] OR "disease werlhof"[Title/Abstract] OR "werlhof s disease"[Title/Abstract] OR (("Disease"[MeSH Terms] OR "Disease"[All Fields] OR "diseases"[All Fields] OR "disease s"[All Fields] OR "diseased"[All Fields]) AND "Werlhof's"[Title/Abstract]) OR ("Disease"[Title/Abstract]) OR "autoimmune thrombocytopenia"[Title/Abstract] OR "autoimmune thrombocytopenias"[Title/Abstract] OR "thrombocytopenia autoimmune"[Title/Abstract] OR "thrombocytopenias autoimmune"[Title/Abstract] OR "autoimmune thrombocytopenic purpura"[Title/Abstract] OR (("Autoimmune"[All Fields] OR	

		"autoimmunity"[MeSH Terms] OR "autoimmunity"[All Fields] OR "autoimmunities"[All Fields] OR "autoimmunization"[All Fields] OR "autoimmunizing"[All Fields]) AND "thrombocytopenic purpuras"[Title/Abstract]) OR (("Purpura"[MeSH Terms] OR "Purpura"[All Fields] OR "Purpuras"[All Fields]) AND "autoimmune thrombocytopenic"[Title/Abstract]) OR (("Purpura"[MeSH Terms] OR "Purpura"[All Fields] OR "Purpuras"[All Fields]) AND "autoimmune thrombocytopenic"[Title/Abstract]) OR (("Purpura"[MeSH Terms] OR "Purpura"[All Fields] OR "Purpuras"[All Fields]) AND "thrombocytopenic autoimmune"[Title/Abstract])) AND ((y_5[Filter]) AND (guideline[Filter]))	

Appendix C. ITP Treatment Algorithm

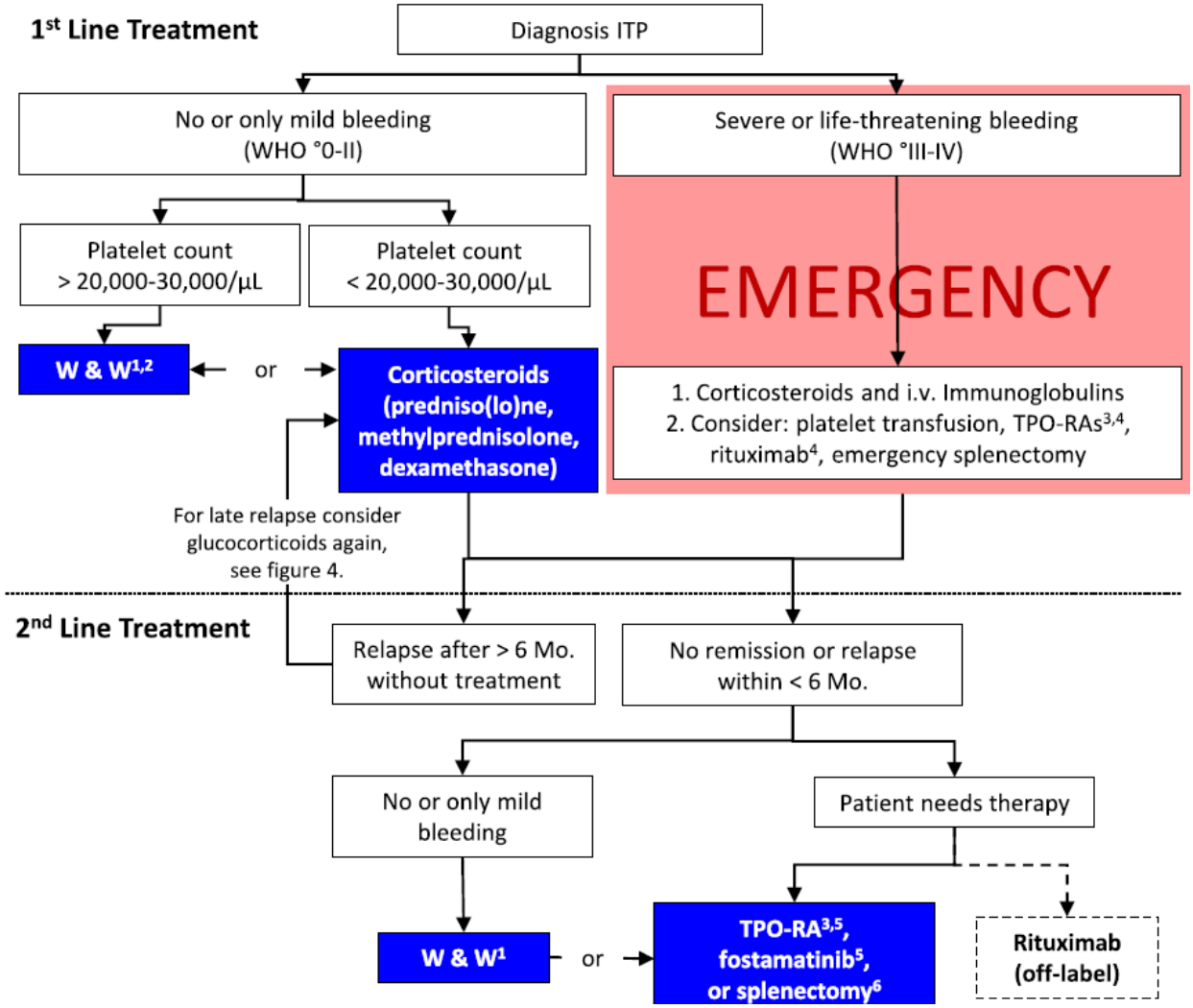

Figure 1. *ITP Treatment Algorithm by Expert Group from Austria, Germany, and Switzerland*

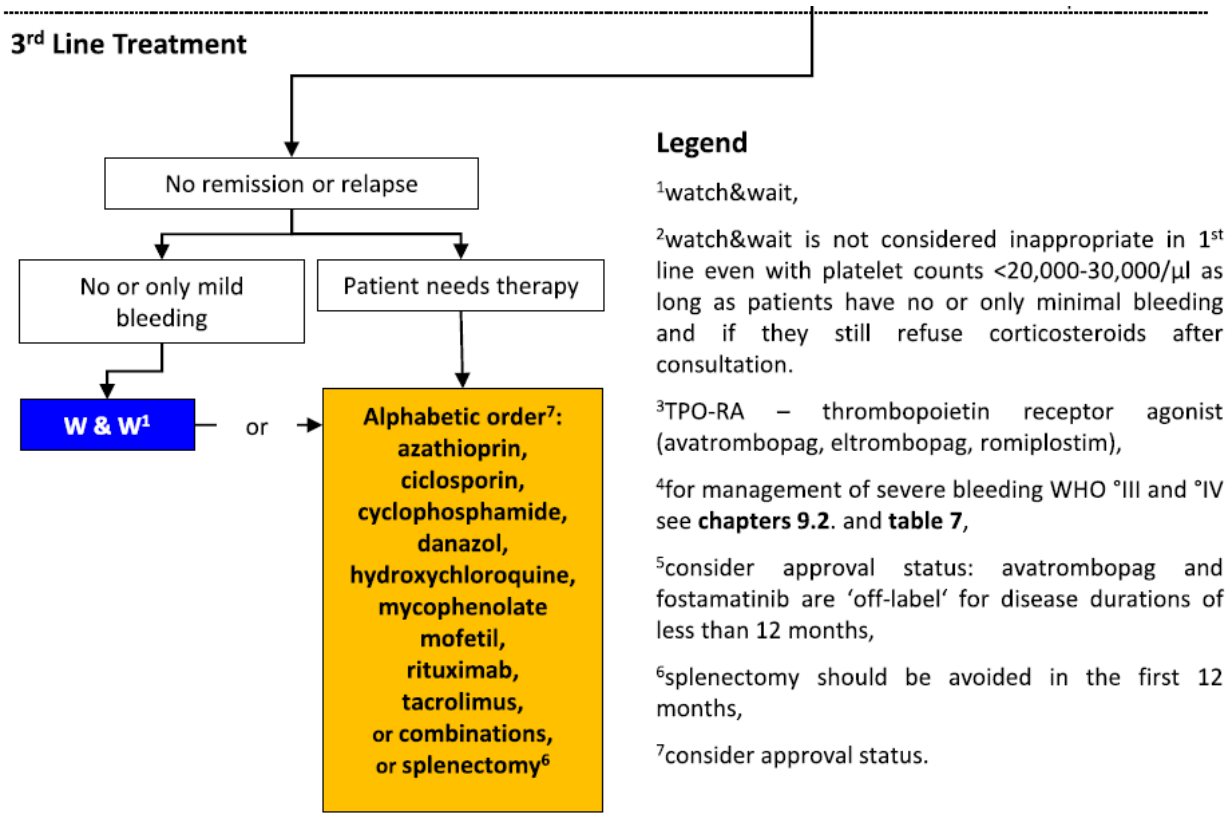

Figure 2. *ITP Treatment Algorithm by Expert Group from Austria, Germany, and Switzerland (cont'd)*

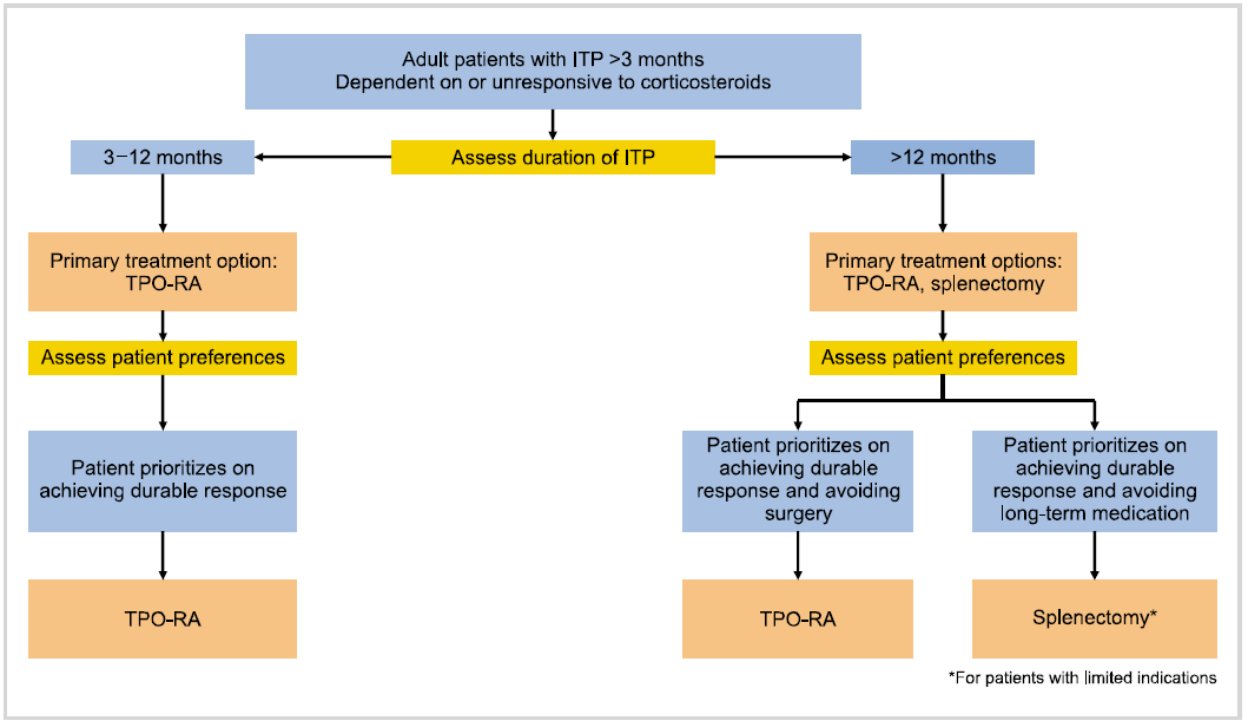

Figure 3. *Korean 2022 Algorithm for the Selection of Second-Line Therapy in Adult Patients with ITP*