Incorporating ITP guidelines into practice

- **The American Society of Hematology (ASH) updated its guidelines in 2019**
  - The multidisciplinary panel of authors included experts in both adult and pediatric ITP, as well as patient representatives
  - These evidence-based guidelines are intended to support clinicians, patients, and other health care professionals in decisions surrounding management of ITP
- **The International Consensus Report (ICR) published an update of its 2010 recommendations**
  - The ICR expert panel based the update on a review of all relevant articles from 2009 to 2018
  - Guidance on diagnosis and management of ITP in adults and children is provided, highlighting the role of quality of life in treatment decisions

ITP, immune thrombocytopenia.

Indication and Important Safety Information

Indication for PROMACTA® (eltrombopag)

PROMACTA is indicated for the treatment of thrombocytopenia in adult and pediatric patients 1 year and older with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. PROMACTA should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding.

Limitations of Use

PROMACTA is not indicated for the treatment of patients with myelodysplastic syndromes (MDS).

Safety and efficacy have not been established in combination with direct-acting antiviral agents used without interferon for treatment of chronic hepatitis C infection.

Important Safety Information for PROMACTA® (eltrombopag)

WARNING: RISK FOR HEPATIC DECOMPENSATION IN PATIENTS WITH CHRONIC HEPATITIS C
In patients with chronic hepatitis C, PROMACTA in combination with interferon and ribavirin may increase the risk of hepatic decompensation.

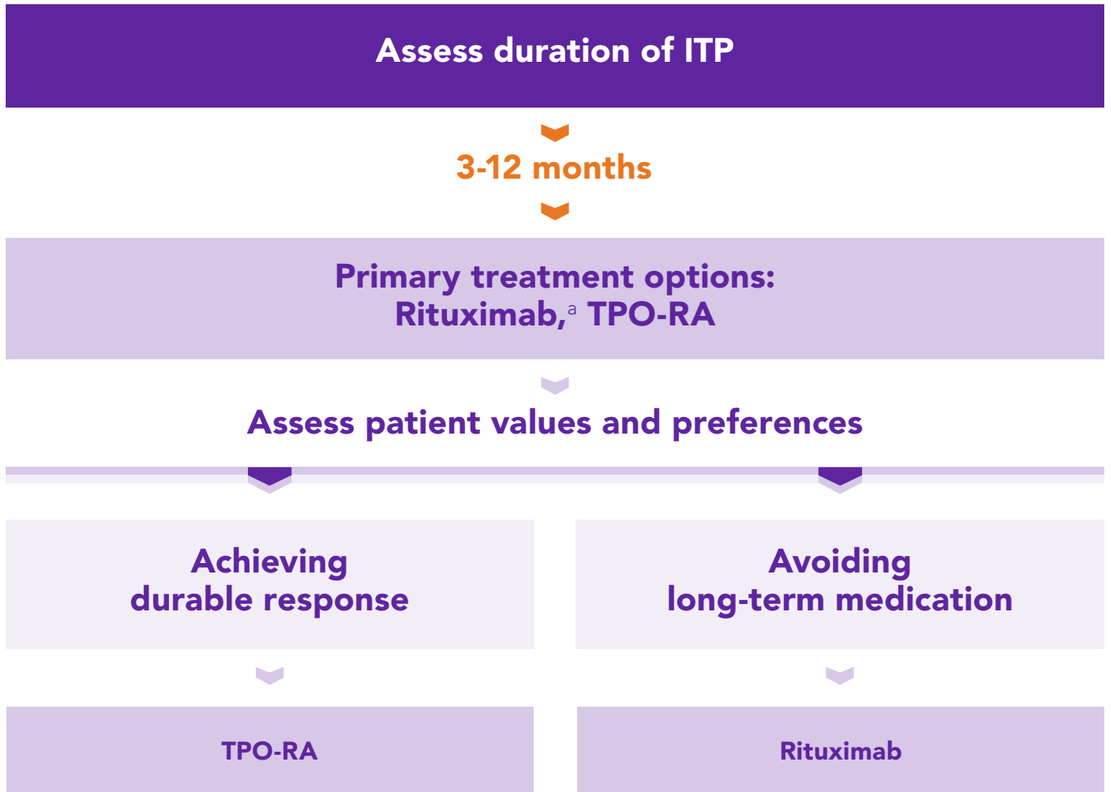
RISK OF HEPATOTOXICITY
PROMACTA may increase the risk of severe and potentially life-threatening hepatotoxicity. Monitor hepatic function and discontinue dosing as recommended.

Please see additional Important Safety Information for PROMACTA throughout, and click here for full Prescribing Information, including Boxed WARNING, and Medication Guide.

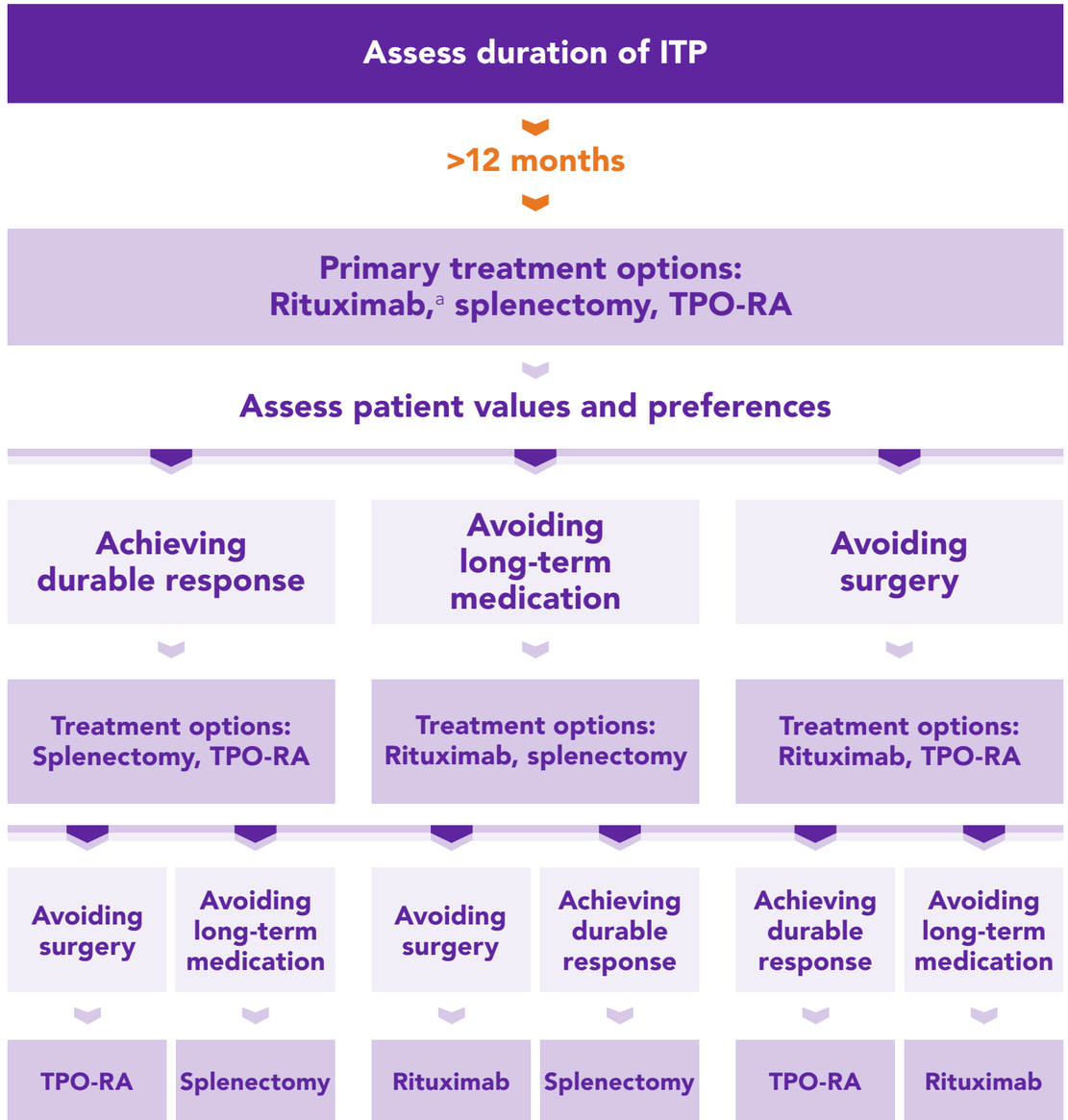
Once-daily oral
PROMACTA®
(eltrombopag)
12.5mg, 25mg, 50mg, 75mg tablets
12.5mg, 25mg oral suspension

For adults with ITP ≥3 months who failed first-line therapy and place a high value on durable response*…

ASH guidelines suggest a TPO-RA as a preferred second-line option[1]



[a]Rituximab is not FDA approved for use in ITP.[2]



FDA, US Food and Drug Administration; TPO-RA, thrombopoietin receptor agonist.

*The 2019 ASH guidelines define *durable response* as a platelet count ≥30,000/mcL and at least doubling of the baseline count at 6 months.[1]

Important Safety Information for PROMACTA® (eltrombopag) (continued)

Hepatotoxicity

PROMACTA may increase the risk of severe and potentially life-threatening hepatotoxicity.

Treatment of ITP, chronic hepatitis C, and refractory severe aplastic anemia

- Measure serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin prior to initiation of PROMACTA, every 2 weeks during the dose-adjustment phase, and monthly following establishment of a stable dose

Please see additional Important Safety Information for PROMACTA throughout, and click here for full Prescribing Information, including Boxed WARNING, and Medication Guide.

Short courses of steroids are recommended—no more than 6 to 8 weeks[1,3]

Duration of corticosteroid therapy in newly diagnosed adults with ITP

The ASH guidelines panel recommends[1]:

- A short initial course (≤6 weeks including treatment and taper) of prednisone and against a prolonged course (>6 weeks)
  - The ASH guidelines panel further advises the treating physician to conduct an assessment of the impact on HRQoL (depression, fatigue, mental status, etc) for all patients receiving corticosteroids

The ICR experts state[3]:

- If a response (defined as ≥50,000/mcL) is seen, predniso(lo)ne should be tapered, aiming to stop by 6 weeks—even if the platelet count drops during the taper
  - If no response is seen within 2 weeks, treatment should be tapered rapidly over 1 week and stopped

"The panel agreed that a longer course of steroids would likely not be acceptable to patients given the impact of corticosteroids on mood, sleep, weight gain, and other side effects."[1]

—ASH guidelines panel

"Probably the most consistent and prevalent error in ITP management is overusage and reliance on steroids."[3]

—ICR expert panel

Guidelines suggest delaying splenectomy and prioritizing patient preference[1,3]

Experts recommend delaying splenectomy at least 1 year after diagnosis[1,3]

According to the ASH guidelines panel[1]:

- Splenectomy should be delayed at least 1 year after diagnosis because of the potential for spontaneous remission in the first year

The ICR experts go even further[3]:

- It is recommended to wait ≥1 to 2 years from diagnosis before performing splenectomy because of the chance of remission or stabilization

"Splenectomy is recommended only after failure of medical therapies and depending on patient age and comorbidities."[3]

—ICR expert panel

A successful second-line treatment plan should consider individual patient preferences[1,3]

The ASH guidelines panel states[1]:

- Patient education and shared decision making are encouraged
- Selection of second-line therapy in adults with ITP should be individualized based on duration of disease and patient values and preferences

The ICR experts highlight[3]:

- Treatment goals should be individualized to the patient and phase of disease
- Patients must be educated on clinical treatment goals and reassured so they can continue normal activities

"Clinicians must make decisions on the basis of the clinical presentation of each individual patient, ideally through a shared decision-making process that considers the patient's values and preferences with respect to the anticipated outcomes of the chosen option."[1]

—ASH guidelines panel

HRQoL, health-related quality of life.

Important Safety Information for PROMACTA® (eltrombopag) (continued)

Hepatotoxicity (continued)

Treatment of ITP, chronic hepatitis C, and refractory severe aplastic anemia (continued)

- PROMACTA inhibits UGT1A1 and OATP1B1, which may lead to indirect hyperbilirubinemia. If bilirubin is elevated, perform fractionation
- Evaluate abnormal serum liver tests with repeat testing within 3 to 5 days. If the abnormalities are confirmed, monitor serum liver tests weekly until resolved or stabilized

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Shared decision making based on patient preference is important in second line[1,3]

Treatment goals should be tailored to the patient[3]

The ICR experts recommend:

1. Treatment goals should be individualized to the patient and phase of disease
2. Treatment should prevent severe bleeding episodes
3. Treatment should maintain a target platelet level >20,000/mcL to 30,000/mcL at least for symptomatic patients (because risk for major bleeding increases below this level)
4. Treatment should be with minimal toxicity
5. Treatment should optimize HRQoL

ICR highlights that the main goal of treatment is to attain a durable increase in the platelet count while minimizing AEs[3]

Both ASH and ICR call out…

Key components in the treatment decision[1,3]

Clinical Parameters
- Age
- Duration of ITP
- Frequency/extent of bleeding episodes
- Need for rescue medication

Quality-of-Life Parameters
- Activity and lifestyle
- Fatigue
- Medical and social support
- Patient values and preferences

TPO-RAs are a preferred second-line treatment option[1,3]

For patients who value a durable response and want to avoid surgery, look to a TPO-RA[1,3]

- **The ASH guidelines panel suggests a TPO-RA rather than rituximab**[1]
  - The panel specifies eltrombopag or romiplostim; this is not a classwide recommendation
- **The ICR experts note an additional benefit of TPO-RAs**[3]
  - Patients responding to TPO-RAs also demonstrated improved HRQoL—with responders improving more than responders to other therapies evaluated

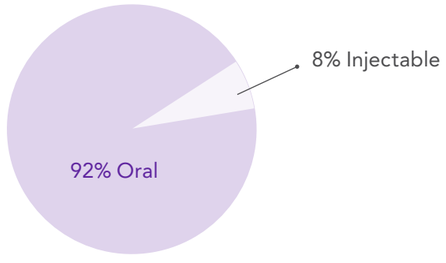
Route of administration is a key consideration in the choice of TPO-RA[1]

- The ASH guidelines note that individual patient preference may place a higher value on the use of an oral medication rather than an injection

"Patient preference for route of administration, that is, oral daily medication compared with weekly subcutaneous injection, will likely drive decision making."[1]

—ASH guidelines panel

Given a choice, patients prefer oral dosing[4]



Patient administration preference

In the global I-WISh survey, ITP patients were asked to select their preference in terms of how they would like to take their ITP medication if given the choice.

Results are based on 501 patients in the United States involved in the I-WISh survey conducted in 13 countries.

Patients did not show a preference for a specific product and may or may not have had experience with any therapeutic option for ITP.

AEs, adverse events; I-WISh, ITP World Impact Survey.

Important Safety Information for PROMACTA® (eltrombopag) (continued)

Hepatotoxicity (continued)

Treatment of ITP, chronic hepatitis C, and refractory severe aplastic anemia (continued)

- Discontinue PROMACTA if ALT levels increase to ≥3 times the upper limit of normal in patients with normal liver function or ≥3 times baseline in patients with pretreatment elevations in transaminases and are progressively increasing; or persistent for ≥4 weeks; or accompanied by increased direct bilirubin; or accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation

Please see additional Important Safety Information for PROMACTA throughout, and click here for full Prescribing Information, including Boxed WARNING, and Medication Guide.

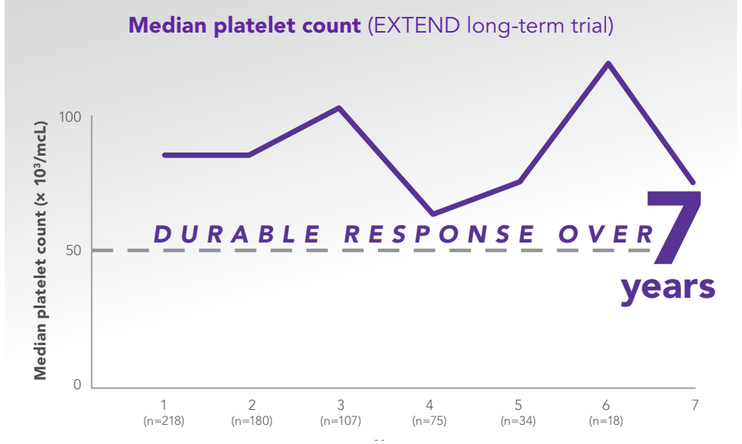
For your adult patients with persistent or chronic ITP who failed their first therapy…

Did you know PROMACTA reported the longest results in the largest trial (EXTEND) ever in persistent or chronic ITP?[5-9]

For second-line patients who want a durable response, ASH guidelines suggest a TPO-RA[1]

PROMACTA demonstrated…

Up to 7 years of durable platelet response[5,6]



- In the primary end point, no new adverse reactions were identified at 6 years of therapy[5,6]

The open-label EXTEND study evaluated long-term safety and efficacy of eltrombopag in adults with ITP who had completed a previous eltrombopag study.[5,6,10] Interim results showed that treatment with eltrombopag was effective in maintaining platelet counts up to 3 years.[10] This study reviewed more than 8 years of continuous treatment.[6,10] Of 302 patients enrolled, 135 (45%) completed the study; 60% were treated at least 2 years and 35% at least 3 years.[6,10] The "n" value represents the total number of patients, with median platelet counts ≥50,000/mcL by Week 2 and at least that throughout.[5,6,10]

No new adverse reactions at 6 years in the long-term study[5,6]

- 302 patients were enrolled in the EXTEND trial; not all patients were evaluable at 6 years[5]
  - Primary end points were safety and tolerability assessed via laboratory tests[6]

Adverse Reactions (≥3%)	PROMACTA 50 mg (N=302)[5]
Headache	10%
ALT increased	5%
AST increased	5%
Cataracts	5%
Fatigue	5%
Blood bilirubin increased	4%
Nausea	4%
Hyperbilirubinemia	3%
Diarrhea	3%

- No increased risk of venous thromboembolism with PROMACTA® (eltrombopag) in the EXTEND study[6]
- No new safety signals, despite increased duration of exposure to eltrombopag[6]
- No increase in incidence of previously identified safety concerns (thromboembolic events and hepatobiliary laboratory abnormalities)[6]
- No clinically relevant increase in bone marrow reticulin or collagen fibers[6]

Important Safety Information for PROMACTA® (eltrombopag) (continued)

Hepatotoxicity (continued)

Treatment of ITP, chronic hepatitis C, and refractory severe aplastic anemia (continued)

- If the potential benefit for reinitiating treatment with PROMACTA outweighs the risk for hepatotoxicity, then consider cautiously reintroducing PROMACTA and measure serum liver tests weekly during the dose-adjustment phase. Hepatotoxicity may reoccur if PROMACTA is reinitiated. If liver test abnormalities persist, worsen, or recur, then permanently discontinue PROMACTA

Please see additional Important Safety Information for PROMACTA throughout, and click here for full Prescribing Information, including Boxed WARNING, and Medication Guide.

See the convenience of once-daily oral dosing with PROMACTA[5]

The majority of patients start and stay on a 50-mg dose[5,11]

Starting dose:

Initiate at 50 mg/day[5,a]

If after at least 2 weeks platelet count is **<50,000/mcL**

Titrate up to 75 mg/day[b]

If platelet counts are:

≥200,000/mcL to ≤400,000/mcL at any time	**>400,000/mcL**	**>400,000/mcL** after 2 weeks of therapy at lowest dose of PROMACTA
Decrease daily dose by 25 mg[c]	**Stop PROMACTA**[d]	**Discontinue PROMACTA**

[a]For patients of Asian ancestry, initiate at 25 mg/day. For patients with mild, moderate, or severe hepatic impairment, initiate at a reduced dose of 25 mg once daily; for patients of Asian ancestry with hepatic impairment, consider initiating at a reduced dose of 12.5 mg once daily.[5]

[b]Do not exceed a dose of 75 mg daily. For patients taking 25 mg once daily, increase daily dose by 25 mg; for patients taking 12.5 mg once daily, increase the dose to 25 mg daily before increasing the dose amount by 25 mg.[5]

[c]Wait 2 weeks to assess the effects of this and any subsequent dose adjustments. For patients taking 25 mg once daily, decrease the dose to 12.5 mg once daily.[5]

[d]Increase the frequency of platelet monitoring to twice weekly. Once the platelet count is <150,000/mcL, reinitiate therapy at a daily dose reduced by 25 mg. For patients taking 25 mg once daily, reinitiate therapy at a daily dose of 12.5 mg.[5]

- Monitor clinical hematology and liver tests regularly throughout therapy[5]
- If platelet counts do not increase to a level sufficient to avoid clinically important bleeding after 4 weeks at 75 mg, discontinue therapy[5]

Patients can take PROMACTA without food or with food that is low in calcium (≤50 mg)[5]

- PROMACTA should be taken 2 hours before or 4 hours after medications such as antacids and mineral supplements or foods high in calcium

PROMACTA offers the option of a once-daily oral formulation[5]

- Any time of day[5]
- No need for office visits for weekly injections and less drug wastage[5,12]

With 2 oral formulations, PROMACTA is available even for patients who have difficulty swallowing a pill[5]

Tablets not actual size.

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

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Important Safety Information for PROMACTA® (eltrombopag) (continued)

Thrombotic/Thromboembolic Complications

- Thrombotic/thromboembolic complications may result from increases in platelet counts with PROMACTA
- Reported thrombotic/thromboembolic complications included both venous and arterial events, and were observed at low and at normal platelet counts
- Portal vein thrombosis has been reported in patients with chronic liver disease receiving PROMACTA
- To minimize the risk for thrombotic/thromboembolic complications, do not use PROMACTA in an attempt to normalize platelet counts. Follow the dose-adjustment guidelines to achieve and maintain target platelet counts

Increased Risk of Death and Progression of Myelodysplastic Syndromes (MDS) to Acute Myeloid Leukemia (AML)

- In a clinical trial of patients with intermediate- to high-risk MDS and thrombocytopenia receiving PROMACTA, an increased number of progressions from MDS to AML and deaths have been observed compared to placebo
- PROMACTA is not indicated for the treatment of patients with MDS

Cataracts

- Development or worsening of cataracts with PROMACTA has been reported with a frequency of 5% to 11% in 6 clinical studies
- Perform a baseline ocular examination prior to initiating PROMACTA. Regularly monitor patients for signs and symptoms of cataracts while on PROMACTA

Laboratory Monitoring

- Monitor serum liver tests
- During therapy with PROMACTA, assess complete blood counts (CBCs) with differentials, including platelet counts, weekly until a stable platelet count has been achieved. Monitor platelet counts monthly thereafter
- Obtain CBCs with differentials, including platelet counts, weekly for at least 4 weeks following discontinuation of PROMACTA
- When switching between the oral suspension and tablet, assess platelet counts weekly for 2 weeks, then follow standard monthly monitoring

Drug/Drug and Drug/Food Interactions

- PROMACTA must be taken at least 2 hours before or 4 hours after any medications or products containing polyvalent cations such as antacids, calcium-rich foods, and mineral supplements
- Take PROMACTA without a meal or with a meal low in calcium (≤50 mg)

Adverse Reactions

Across all indications, the most common adverse reactions (≥20% in any indication) were anemia, nausea, pyrexia, ALT increased, cough, fatigue, headache, and diarrhea.

The most common adverse reactions in 3 placebo-controlled clinical trials in patients with persistent or chronic ITP (≥3% and greater than placebo) for PROMACTA were nausea (9%), diarrhea (9%), upper respiratory tract infection (7%), vomiting (6%), increased ALT (5%), myalgia (5%), urinary tract infection (5%), oropharyngeal pain (4%), increased AST (4%), pharyngitis (4%), back pain (3%), influenza (3%), paresthesia (3%), and rash (3%).

The most common adverse reactions in 2 placebo-controlled clinical trials in patients with persistent or chronic ITP 1 year and older (≥3% and greater than placebo) for PROMACTA were upper respiratory tract infection (17%), nasopharyngitis (12%), cough (9%), diarrhea (9%), pyrexia (9%), abdominal pain (8%), oropharyngeal pain (8%), toothache (6%), ALT increased (6%), rash (5%), AST increased (4%), and rhinorrhea (4%).

References:

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10. Wong RSM, Saleh MN, Khelif A, et al. Safety and efficacy of long-term treatment of chronic/persistent ITP with eltrombopag: final results of the EXTEND study. *Blood.* 2017;130(23):2527-2536.
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13. Doptelet [prescribing information]. Durham, NC: Dova Pharmaceuticals Inc; 2020.

APLD, anonymous patient-level data.

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For your adult patients with persistent or chronic ITP who failed their first therapy…

How does PROMACTA fit with the experts' guidelines?[1,3,5]

Durable platelet response (up to 7 years)[5,6]

- The longest results ever reported in adults with persistent or chronic ITP[5-9]

Consistent safety profile[5,6]

- All adverse reactions in the long-term trial were ≤10%—with no new adverse reactions identified at 6 years[5,6]
- Most common adverse reactions included headache, increased ALT or AST, cataracts, fatigue, increased blood bilirubin, nausea, hyperbilirubinemia, and diarrhea[5]

Convenient once-daily oral dosing[5]

- PROMACTA® (eltrombopag) is the only TPO-RA available in an oral suspension formulation for patients who have difficulty swallowing a pill (12.5 mg, 25 mg available)[5,12,13]

Patient portrayal.

PROMACTA is indicated for patients with persistent or chronic ITP, as early as 3 months after diagnosis, after first treatment failure.[5] Ask your patients about their preferences.

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NOVARTIS

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12.5mg, 25mg oral suspension

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080