Subject: Promacta (eltrombopag): Chronic Immune (idiopathic) Thrombocytopenic Purpura

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This Medical Policy is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina medical coverage policy (MCP) document and provide the directive for all Medicare members.

SUMMARY OF EVIDENCE/POSITION

This policy addresses the coverage of Promacta (eltrombopag) for the treatment of thrombocytopenia in individuals with chronic immune thrombocytopenia (ITP) when appropriate criteria are met.

- Eltrombopag (Promacta) is a thrombopoietin (TPO) receptor agonist, used to increase platelet production in patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

- Eltrombopag provides an option for those patients who no longer have platelet responses to corticosteroids, immune globulin or splenectomy, and provides an option in those patients who are not candidates for splenectomy, who cannot tolerate corticosteroids nor have contraindications to their long-term use.

- Eltrombopag has only been studied in patients for whom standard ITP treatments have been ineffective such as corticosteroids, immune globulin therapy (IVIG), rituximab, chemotherapy (e.g., cyclophosphamide, vincristine), danazol, and azathioprine, as well as splenectomy. Steroids and/or splenectomy are considered first-line treatments of choice for chronic ITP.

- There are no studies evaluating the efficacy of eltrombopag compared to other refractory ITP treatment options, such as romiplostim (Nplate).

- There are no clinical studies directly comparing the safety and efficacy of the two thrombopoietin (TPO) receptor agonist for the treatment of ITP, eltrombopag (Promacta) and romiplostim (Nplate); both remain second-line therapy. Trials of romiplostim were conducted in patients refractory to standard treatments, defined as corticosteroids, immunoglobulins, rituximab, cytotoxic therapies, danazol, and azathioprine.
Due to risk of rare but serious side effects and uncertain long term benefit, eltrombopag should only be reserved for very refractory patients when other treatments options have been ineffective. Eltrombopag may cause hepatotoxicity; therefore, caution is advised for members with preexisting hepatic disease.

It is uncertain whether the increase in platelets with eltrombopag is sustainable and whether eltrombopag decreases long-term rate of bleeding episodes or other complications in patients with chronic ITP.

- There is low-certainty evidence from one 80-week open-label study in 207 patients with chronic ITP that suggests that the effectiveness of eltrombopag may decrease significantly over time. At week 52, only 2 out of 207 patients were able to maintain platelet count >50,000/mm³ continuously.\(^a,8\)
- A Phase III, double-blind, placebo-controlled trial\(^a,9\) in adults with previously treated ITP for more than 6 months’ duration who had baseline platelet counts < 30 x 10⁹/L were randomized in a 2:1 ratio to standard-of-care treatment plus Promacta 50 mg QD (n = 135) or placebo (n = 62) for 6 months. The Promacta dose was adjusted based on individual platelet counts. The primary endpoint was achieving a platelet count ≥ 50 x 10⁹/L and ≤ 400 x 10⁹/L. A total of 106 patients given Promacta (79%) responded to treatment at least once during the study compared with 17 patients (28%) in the placebo group. A sustained platelet response (platelet count ≥ 50 x 10⁹/L and ≤ 400 x 10⁹/L for 6 out of the last 8 weeks of the 26-week treatment period without rescue medication use) was obtained by 60% given Promacta vs. 10% of patients given placebo.\(^1\) Other benefits have also been noted for Promacta (e.g., fewer patients required rescue therapy, less clinically significant bleeding).\(^a,9\) Extension studies have also been performed with Promacta; 210 patients have completed 12 months of therapy and 138 have undergone 24 months of therapy.\(^a\)

Although extension studies have also been performed with Promacta, the effect on overall survival is unknown, given the lack of evidence.\(^8\)

The efficacy and safety of Promacta in pediatric patients ages one to 17 years with chronic ITP was evaluated in two double-blind, placebo-controlled trials of 159 participants where the primary endpoint was an increase in platelet counts. In the first trial (n=67), patients were randomly assigned to receive either Promacta or placebo daily for seven weeks. Of those taking Promacta, 62 percent had an improvement in platelet counts without rescue therapy between weeks one and six, compared to 32 percent in the placebo group. In the second trial (n=92), patients received either Promacta or placebo daily for 13 weeks and in those treated with Promacta, 41 percent experienced increased platelet counts for at least six out of eight weeks between weeks five to 12, compared to 3 percent of patients receiving placebo. In both trials, patients taking Promacta also had less need for other treatments to increase their platelet counts, such as corticosteroids or platelet transfusions. Among patients taking one or more ITP medications at the start of the trials, about half were able to reduce or discontinue their use of these medications, primarily corticosteroids.

The most common side effects of treatment with Promacta in children ages one and older were infections of the upper respiratory tract or nose and throat (symptoms including fever, cough, nasal congestion, runny nose and sore throat), diarrhea, abdominal pain, rash and increase in liver enzymes.

The safety and efficacy of Promacta in pediatric patients younger than one year with ITP, or in pediatric patients with thrombocytopenia associated with chronic hepatitis C and severe aplastic anemia, have not been established.

**CLASSIFICATION:** Thrombopoietin receptor agonist
Promacta (eltrombopag) is indicated for the treatment of:

- **Chronic immune (idiopathic) thrombocytopenia** in patients with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

- **Chronic hepatitis C infection–associated thrombocytopenia** in adult and pediatric patients 1 year and older with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

- **Severe aplastic anemia** in patients who have had an insufficient response to immunosuppressive therapy.

***NOTE: This policy only addresses the coverage of Promacta (eltrombopag) for the treatment of thrombocytopenia in individuals with **chronic immune thrombocytopenia (ITP)**. Other FDA-approved indications are not addressed in this policy.***

**Available as:**
Tablets: 12.5 mg, 25 mg, 50 mg, 75 mg, and 100 mg
For oral suspension: 25 mg

**FDA Approved:** November 20, 2008

June 2015: Promacta (eltrombopag) approved for the treatment of thrombocytopenia in adult and pediatric patients 6 years and older with chronic immune ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Previously, the treatment of chronic immune ITP was only approved in adults.

August 2015: FDA extended the indication of eltrombopag for ITP in patients at least one year old who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy.

**Black Box Warning**
Hepatic decompensation: In patients with chronic hepatitis C, eltrombopag in combination with interferon and ribavirin may increase the risk of hepatic decompensation.

**Limitations of Use**
- Promacta should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding.
- Promacta should be used only in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy.
- Safety and efficacy have not been established in combination with direct-acting antiviral agents used without interferon for treatment of chronic hepatitis C infection.
Promacta (eltrombopag) may be authorized for members who meet ALL of the following criteria [ALL]

1. Prescriber specialty [ONE]
   - Prescribed by, or in consultation with, a board-certified hematologist or physician specializing in the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP). A,B Submit consultation notes if applicable.

2. Diagnosis/Indication [ALL]
   Clinical documented diagnosis of (includes clinical notes from the member’s medical records including any applicable labs and/or tests, supporting the diagnosis):
   - Diagnosis of chronic immune (idiopathic) thrombocytopenic purpura (ITP); also referred to as immune thrombocytopenia
   - Secondary causes of thrombocytopenia have been ruled out. Refer to Appendix 1 for Causes of Secondary Immune Thrombocytopenia.
   NOTE: Promacta will not be authorized for secondary causes of thrombocytopenia (except ‘chronic hepatitis C infection–associated thrombocytopenia’ and ‘severe aplastic anemia’ which are FDA approved indications of Promacta)

3. Age/Gender/Other restrictions [ALL]
   - One (1) year of age or older
     - The safety and efficacy of Promacta in pediatric patients younger than one year with ITP, or in pediatric patients with thrombocytopenia associated with chronic hepatitis C and severe aplastic anemia, have not been established. A
   - Prescribed for risk of spontaneous bleeding OR in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding (e.g. hypertension, peptic ulcer disease, anticoagulation, recent surgery, head trauma)
   - Promacta (eltrombopag) is prescribed to minimize the risk of bleeding and not used to normalize platelet counts

   NOTE: Promacta should not be used in an attempt to normalize platelet counts. A-C

   NOTE: The goal of treatment for chronic ITP should be to maintain a safe platelet count, not to achieve a normal platelet count. A A normal platelet count in adults ranges from 150,000 to 450,000 platelets per microliter of blood. Thrombocytopenia is defined as platelet count of less than 150,000 platelets per microliter (150,000/mm³, 150 x 10⁹/L, 15 x 10⁹/L, 150,000/ml, 150 K/5L).
   - Symptomatic bleeding or risk factors for bleeding (e.g., uremia, alcoholism, infections, comorbidity, mandated anticoagulation therapy, undergoing a medical or dental procedure with blood loss anticipation)
Documentation of either ONE (1) of the following criteria: [ONE]

- Platelet count less than $20 \times 10^9/L$ (20,000/mm$^3$)
- Platelet count less than $30 \times 10^9/L$ (30,000/mm$^3$) accompanied by symptoms of bleeding
  - Studies have indicated that ITP patients with persistent platelet counts $< 30,000$ mm$^3$ are at risk for life-threatening bleeds$^{3,4}$
  - During the studies for both Promacta (eltrombopag) and Nplate (romiplostim) in patients with chronic ITP, patients had a baseline platelet count of $30,000/mm^3$ ($= 30 \times 10^9/L$ or $30,000/ml$) or less

4. Step/Conservative Therapy/Other condition Requirements [ALL]

American Society of Hematology (2011) recommends thrombopoietin receptor agonists for patients at risk of bleeding who relapse after splenectomy or who have a contraindication to splenectomy and who have failed at least one other therapy.$^A$

- Documented inadequate response [defined as platelets not increased to at least $50 \times 10^9/L$ ($\geq 50,000$ mm$^3$)], intolerance, contraindication, or other clinical rationale for inappropriateness to at least ONE of the following: [AT LEAST ONE]
  - Systemic corticosteroids$^A$ (i.e. prednisone, methylprednisolone, dexamethasone)
  - Intravenous immune globulin (IVIG or IGIV)$^A$
  - Cytotoxic therapy (i.e. azathioprine, cyclophosphamide, vincristine)
  - Immune suppressant therapy (i.e. cyclosporine, mycophenolate mofetil, rituximab)
  - Danazol; dapsone

- Relapse after splenectomy or documented contraindication to splenectomy$^A$
  - Splenectomy for patients who have failed corticosteroid therapy (American Society of Hematology 2011)$^A$

- Promacta (eltrombopag) is not used concurrently with another thrombopoietin receptor agonist [e.g., Nplate (romiplostim)]
  - Eltrombopag may be used with other therapies for ITP, including corticosteroids, danazol, azathioprine, intravenous (IV) immunoglobulin, and anti-D immunoglobulin.

5. Contraindications*/Exclusions/Discontinuations

*Food and Drug Administration (FDA)–approved labeling lists no contraindications to therapy with ivacaftor/lumacaftor.$^a$

Authorization will not be granted if ANY of the following conditions apply [ANY]

- Non-FDA approved indications
- Pediatric patients younger than one year
- Hypersensitivity to eltrombopag or any of its components
- Utilized to normalize platelet counts
- Utilized in individual with ITP whose degree of thrombocytopenia and clinical condition do not increase the risk of bleeding
  - Promacta should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding.
- Concurrent use with another thrombopoietin receptor agonist [e.g., romiplostim (Nplate)]
- Thrombocytopenia from any other causes except chronic ITP, including thrombocytopenia due to myelodysplastic syndrome
Active malignancy or stem cell disorder

6. Labs/Reports/Documentation required [ALL]
   All documentation for determination of medical necessity must be submitted for review. Prescriber to submit medical records and specific labs, chart notes, and documentation as indicated in the criteria above. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

### CONTINUATION OF THERAPY

Promacta (eltrombopag) may be authorized for continuation of therapy if meet ALL of the following criteria are met: [ALL]

1. Initial Coverage Criteria [ALL]
   - Member currently meets ALL initial coverage criteria

2. Compliance [ALL]
   - Dose administered has not exceeded 75 mg/day

3. Labs/Reports/Documentation required [ALL APPLICABLE]
   - Documentation of recent platelet count (within the last 90 days) is either: [ONE]
     - An increase in platelet count over baseline, counts should be greater than $50 \times 10^9/L$ (>30,000/mm$^3$) BUT less than $150 \times 10^9/L$ ($\leq 150,000$/mm$^3$)
     - At least 30,000/mm$^3$ but platelet counts have increased from baseline accompanied with a resolution of previous bleeding
   - Platelet count has increased sufficiently to avoid clinically important bleeding

4. Discontinuation of Treatment [ANY]
   Discontinue treatment if ANY of the following conditions applies: [ANY]
   - Intolerable adverse effects or drug toxicity
   - Persistent and uncorrectable problems with adherence to treatment
   - Poor response to treatment as evidenced by physical findings and/or clinical symptoms
   - Contraindications/Exclusions
     - Non-FDA approved indications
     - Hypersensitivity to eltrombopag or any of its components
     - Concurrent use with another thrombopoietin receptor agonist [e.g., romiplostim (Nplate)]
     - Pediatric patients younger than one year
     - Utilized to normalize platelet counts
     - Utilized in individual with ITP whose degree of thrombocytopenia and clinical condition do not increase the risk of bleeding
       - Promacta should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding.
     - Concurrent use with another thrombopoietin receptor agonist [e.g., romiplostim (Nplate)]
     - Thrombocytopenia from any other causes except chronic ITP, including thrombocytopenia due to myelodysplastic syndrome
Active malignancy or stem cell disorder

- Platelet count is $> 400 \times 10^9/L \ (\geq 400,000 \ /mm^3)^{\text{a}}$
- Platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of therapy at the maximum daily dose of 75mg
- ALT levels increase to $\geq 3X$ upper limit of normal in patients with normal liver function or $\geq 3X$ baseline in patients with pre-treatment elevations in transaminases and are: 1) progressive 2) persistent for $\geq 4$ weeks 3) accompanied by increased direct bilirubin, or 4) accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation

**ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD**

**Promacta (eltrombopag)** may be authorized for continuation of therapy if meet ALL of the following criteria are met: [ALL]

1. **Recommended Dosage [ALL]**

   **Chronic ITP:**

   - Pediatric Patients with ITP aged 1 to 5 Years: Initiate at a dose of 25 mg once daily
   - Initial Dose Regimen: *Adult and Pediatric Patients 6 Years and Older with ITP*: Initiate Promacta at a dose of 50 mg once daily, except in patients who are of East Asian ancestry (such as Chinese, Japanese, Taiwanese, or Korean) or who have mild to severe hepatic impairment (Child-Pugh Class A, B, C).
   - For patients of East Asian ancestry with ITP, initiate at a reduced dose of 25 mg once daily
   - For patients of East Asian ancestry with ITP and hepatic impairment (Child-Pugh Class A, B, C), initiate at a reduced dose of 12.5 mg once daily
   - Initial: 50 mg once daily; adjust dose to achieve and maintain platelet count $\geq 50,000/mm^3$ to reduce the risk of bleeding; maximum dose: 75 mg once daily. 
     - The safety and effectiveness of higher doses have not been established.
   - Use the lowest dose to achieve and maintain a platelet count greater than or equal to $50 \times 10^9/L$ as necessary to reduce the risk for bleeding. Dose adjustments are based upon the platelet count response. Adjust dose based on platelet count response; initial platelet response generally occurs within 1-2 weeks.
   - Treatment for ITP should be discontinued after 4 weeks of use at the maximum daily dose of 75 mg if platelet levels do not increase to a level sufficient to avoid clinically significant bleeding.

*Refer to Appendix 2 for further information on ‘Dose Adjustments of Promacta for Chronic ITP’*
2. **Authorization Limit [ALL]**

- Quantity limit:
  - 12.5 mg and 25 mg: 3 tabs/day
  - 50 mg, 75 mg: 1 tab/day

- Maximum daily dose: 75 mg/day

- Dispensing limit: Only a 1-month supply may be dispensed at a time<sup>e</sup>

- Duration of initial authorization: 4 weeks
  
  **NOTE:** Discontinue if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks at the maximum dose.

- Continuation of treatment: Re-authorization for continuation of treatment is required every 3 months to determine continued need based on documented positive clinical response

3. **Route of Administration [ALL]**

- Eltrombopag is considered a **self-administered** medication

- If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare. Self-administered medications may not be dispensed for self-administration and billed through the medical benefit by a provider; they must be dispensed through a participating pharmacy.

- Prescribers, pharmacies, and patients must enroll in the Promacta CARES program to obtain access to eltrombopag.

### COVERAGE EXCLUSIONS

All other uses of the mentioned drugs that are not an FDA-approved indication or included in ‘Coverage Criteria’ section above are considered **experimental/investigational** and is not a covered benefit.

- Thrombocytopenia in Myelodysplastic Syndrome (MDS)
  - Limited data available currently describing the use of Promacta for thrombocytopenia associated with MDS.
  - Recommendations from the National Comprehensive Cancer Network (NCCN) (Version 2.2014) at the present time do not mention the use of thrombopoietin receptor agonists (e.g., Promacta) in the management of thrombocytopenia in MDS.

SUMMARY

Immune thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by immunologic destruction of otherwise normal platelets most commonly occurring in response to an unknown stimulus. ITP can be classified based on patient age (childhood versus adult), duration of illness (acute versus chronic), and presence of an underlying disorder (primary versus secondary). Primary ITP occurs in isolation, whereas secondary ITP occurs in association with other disorders. Secondary causes include autoimmune, or secondary immune thrombocytopenic purpura, is associated with other underlying conditions, such as autoimmune disorders (e.g., systemic lupus erythematosus, antiphospholipid syndrome, Graves disease, sarcoidosis), lymphoproliferative disorders, infections (e.g., human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, varicella-zoster virus, hepatitis C virus, Helicobacter pylori) or medications [e.g., valproic acid (Depakote), gold salts, heparin]. The current best estimate indicates that ITP is diagnosed at a rate of 3.3 per 100,000 adults per year. An International Working Group (IWG) consensus panel of both adult and pediatric experts in ITP recently provided policy on terminology, definitions, and outcome criteria for this disorder. Primary ITP was defined by the IWG as a platelet count less than 100 x 10^9/L in the absence of other causes or disorders that may be associated with thrombocytopenia. The American Society of Hematology defines ITP as isolated thrombocytopenia (low platelet count with otherwise normal results on complete blood count and peripheral blood smear) in a patient with no clinically apparent associated conditions or factors that can cause thrombocytopenia (such as infection with the human immunodeficiency virus [HIV], systemic lupus erythematosus, lymphoproliferative disorders, myelodysplasia, agammaglobulinemia, therapy with certain drugs, alloimmune thrombocytopenia, and congenital or hereditary thrombocytopenia). An abnormal blood count or peripheral blood smear due to a coexisting non-immune condition (such as iron deficiency or thalassemia minor) does not, in itself, exclude the diagnosis of ITP.

There are two types of ITP, acute (temporary or short-term) and chronic (long-lasting). Acute ITP generally lasts less than 6 months. It mainly occurs in children, both boys and girls, and is the most common type of ITP. It often occurs after an infection caused by a virus. Chronic ITP is long-lasting (6 months or longer) and mostly affects adults. However, some teenagers and even younger children can get this type of ITP. Chronic ITP affects women 2 to 3 times more often than men. Treatment depends on how severe the bleeding symptoms are and the platelet count. In mild cases, treatment may not be needed.

No specific criteria establish the diagnosis of ITP; the diagnosis relies on the exclusion of alternative disorders or underlying conditions, such as autoimmune disorders (e.g., systemic lupus erythematosus, antiphospholipid syndrome, Graves disease, sarcoidosis), lymphoproliferative disorders, infections (e.g., human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, varicella-zoster virus, hepatitis C virus, Helicobacter pylori) or medications (e.g., valproic acid (Depakote), gold salts, heparin). Refer to Appendix 1 for Causes of Secondary Immune Thrombocytopenia.

There is no “gold standard” diagnostic test to confirm an ITP diagnosis. However, the approach to diagnosis starts with a thorough patient/family history and physical examination to identify evidence of bleeding. Therefore, alternative causes of thrombocytopenia should also be considered before making a diagnosis of ITP.

A normal platelet count in a healthy person is between 150,000 and 400,000/mm^3. The primary goal of treatment is to sustain a platelet count associated with adequate hemostasis to prevent serious or major bleeding. Normalizing platelet counts is NOT a goal of treatment.

Current treatments for ITP include corticosteroids, IV immune globulin, or Rho(D) immune globulin, which all act by interfering with platelet destruction. Corticosteroids are considered first-line treatment and increase platelet counts usually within one week of initiation. Intravenous immune globulin and rituximab (Rituxan) also have been used for...
Thrombopoietin receptor agonists [e.g., eltrombopag (Promacta) and romiplostim (Nplate)]

Thrombopoietin (TPO)-receptor agonists work by stimulating megakaryocytes from bone marrow progenitor cells, leading to platelet formation. The two TPO agonists currently available are Promacta® (eltrombopag) oral tablets and Nplate® (romiplostim) subcutaneous injection.

Eltrombopag is an oral nonpeptide-selective, thrombopoietin-receptor agonist. It activates intracellular signal-transduction pathways, leading to increased proliferation and differentiation of megakaryocytes from bone marrow progenitor cells. Eltrombopag does not affect platelet aggregation or platelet activation. Eltrombopag does not increase proliferation in leukemia or solid tumor cell lines; a reduction in proliferation has been observed in a variety of solid and hematologic tumor cell lines tested.

Administration of both romiplostim and eltrombopag increases the risk for development or progression of reticulin fiber deposition within the bone marrow. Discontinuation of romiplostim and eltrombopag may result in thrombocytopenia of greater severity than was present prior to therapy. This worsened thrombocytopenia may increase the patient’s risk of bleeding, particularly if romiplostim or eltrombopag is discontinued while the patient is on anticoagulants or antiplatelet agents.

GUIDELINES

- Guidelines support the use of eltrombopag in chronic ITP refractory to standard therapies and rescue therapies, and close management by a hematologist.

- The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia provided policy for treatment using thrombopoietin receptor agonists:
  - Recommendations included treatment "for adults at risk of bleeding who relapse after splenectomy or who have a contraindication to splenectomy and who have failed at least one other therapy.
  - Studies of thrombopoietin receptor agonists in children and adolescents are under way, but results have not been published. Thus, no recommendations for the use of these agents can be made at this time. Studies are ongoing, but there are no published data to guide the use of these agents in children.
  - A normal platelet count in a healthy person is between 150,000 and 400,000/mm$^3$. The goal of treatment for chronic ITP should be to maintain a safe platelet count, not to achieve a normal platelet count.
  - Risk of spontaneous bleeding increases as platelet counts drops below 20,000 per mm$^3$.
  - Standard of care therapies are effective for many patients with chronic ITP.
    - Around one-third of patients may expect a long-term response from treatment with an oral corticosteroid. Corticosteroids should be rapidly tapered and stopped in patients who fail to respond after 4 weeks.
    - Up to two-thirds of patients with ITP who undergo splenectomy may achieve a normal platelet count, which is often sustained with no additional therapy.

Pivotal Efficacy Studies

The short-term use of eltrombopag was evaluated in two randomized, placebo-controlled trials. Each trial enrolled adults with a chronic ITP history of at least 6 months duration. These adults also had received at least one prior therapy for ITP and had pretreatment platelet counts $< 30 \times 10^9$/L ($< 30,000$ mm$^3$).

  - Multicenter, randomized, double-blind, placebo-controlled trial; 114 patients randomly assigned 2:1 to receive standard of care or eltrombopag 50mg or placebo daily for up to 6 weeks.
Inclusion criteria: Age > 18 years; > 6 month history of ITP, received at least one previous treatment for ITP; pretreatment platelet count < 30,000 mm$^3$; those receiving other ITP maintenance therapies were eligible if doses were stable > 1 month and remained stable throughout the study; new ITP therapies were only permitted in emergency situations; prior therapies with immune globulins, immune modulators, rituximab and cyclophosphamide must have been completed > 2 weeks before enrollment; creatinine and liver enzymes within normal limits

Exclusion criteria: Conditions such as HIV, hepatitis B or C infections, CHF, arrhythmia or thrombosis in prior year, MI within 3 months, women nursing or pregnant, patients requiring use of calcium or magnesium-containing drugs

Baseline characteristics: Median age of 48 years (range, 19-84); 61% were women; 39% had undergone splenectomy; 43% were receiving concomitant ITP medications (75% prednisone); 48% with baseline platelet count < 15,000 mm$^3$; other ITP therapies included IVIG and rituximab

The primary endpoint was a platelet count ≥ 50 x 10$^9$/L (> 50,000 mm$^3$) on day 43 (6 weeks after the start of treatment).

Secondary endpoints included any responders during the 6-week treatment period, incidence of bleeding, safety, tolerability and quality of life.

Results indicated that significantly more patients in the eltrombopag arm achieved a platelet count ≥ 50 x 10$^9$/L (> 50,000 mm$^3$) than those in the placebo arm [59 vs. 16%; OR 9.61 (3.31-27.86); p<0.001].

Conclusions: It was concluded that eltrombopag is effective for the management of thrombocytopenia secondary to ITP.

Considerations: Strengths of the trial is that it is a randomized, double-blind, placebo-controlled trial; however, limitations included the 6 weeks length of the trial is short in comparison to the chronic nature of ITP.

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Eltrombopag for the Treatment of Chronic Idiopathic Thrombocytopenic Purpura

Multicenter, randomized, double-blind, placebo-controlled trial of 117 patients were randomly assigned (1:1:1:1 ratio) to receive placebo, eltrombopag 30mg, 50mg or 75mg daily for 6 weeks; treatment was discontinued when platelet count > 200,000 cells/mm$^3$. Subjects were assessed weekly for 6 weeks then at 2-week intervals for 6 weeks after study med discontinued.

Inclusion criteria: Age > 18 years; > 6 month history of ITP, received at least one treatment for ITP, platelet count < 30,000 mm$^3$, those receiving maintenance immunosuppressive agents were eligible if dose had been stable for at least 1 month prior to study entry, values within normal range for neutrophils, reticulocytes, creatinine and liver enzymes

Exclusion criteria: Conditions such as secondary immune thrombocytopenia, < 10g/dL, CHF, arrhythmia, thromboses within prior year, MI within prior 3 months, women pregnant or nursing

Baseline characteristics: Mean age of patients was 50 years; 62% were women; 47% had undergone splenectomy; 32% were receiving concomitant medication for ITP; 74% received > 2 prior treatments for ITP

Safety: The most common adverse effect was headache in all groups; percent of those experiencing grade 3 & 4 adverse events was similar between all study groups; one case of progressive cataracts was noted; one death due to cardiopulmonary failure with sepsis – no thromboemboli were noted on vessels of the kidneys or liver at autopsy.

The primary endpoint was a platelet count > 50,000 mm$^3$ on day 43. Secondary endpoints included safety, tolerability, signs of bleeding, serum thrombopoietin level and health-related quality of life.

Results: The results indicate that at day 43, the subjects in the eltrombopag 50mg and 75mg arms had a significantly better platelet response compared to the placebo arm [70% vs. 11% eltrombopag 50mg vs. placebo; p=0.002] and [81% vs. 11% eltrombopag 75mg vs. placebo; p=0.001].

Conclusions: Daily at doses of eltrombopag 50mg or 75mg are an effective short-term effective treatment for chronic ITP.

Considerations: The strengths of this trial is that it is a multicenter, randomized, double-blind, placebo-controlled design. The limitations of the trial is the endpoint was platelet count on day 43 does not take into account the chronic, persistent nature of ITP
Pediatric Patientsa

- FDA extended the indication of eltrombopag to patients 1 year and older with chronic ITP in August 2015.

The efficacy and safety of Promacta in pediatric patients 1 year and older with chronic ITP were evaluated in two double-blind, placebo-controlled trials. The trials differed in time since ITP diagnosis: at least 6 months versus at least 12 months. During the trials, doses could be increased every 2 weeks to a maximum of 75 mg once daily. The dose of Promacta was reduced if the platelet count exceeded 200 x 10^9/L and interrupted and reduced if it exceeded 400 x 10^9/L.

Patients refractory or relapsed to at least one prior ITP therapy with a platelet count less than 30 x 10^9/L (n = 92) were stratified by age and randomized (2:1) to Promacta (n = 63) or placebo (n = 29). The starting dose for patients aged 6 to 17 years was 50 mg once daily for those at least 27 kg and 37.5 mg once daily for those less than 27 kg, administered as oral tablets. A reduced dose of 25 mg once daily was used for East Asian patients aged 6 to 17 years regardless of weight. The starting dose for patients aged 1 to 5 years was 1.2 mg/kg once daily (0.8 mg/kg once daily for East Asian patients) administered as oral suspension.

- Promacta (eltrombopag) was approved for the treatment of children six years and older with chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy in June 2015.

PETIT and PETIT2 Clinical Trials

PETIT was a Phase II, multi-center, three-part study to investigate the efficacy, safety and tolerability of Promacta in pediatric patients with previously treated chronic ITP. Part 1 was an open label, dose finding study; Part 2 was double-blind and placebo-controlled, and Part 3 was an open-label extension. The primary endpoint, which was percentage of participants who achieved a platelet count >=50 Gi/L without rescue therapy at least once between Weeks 1 and 6, was met by 63% and 18% of Promacta and placebo patients, respectively (p=0.0043). The secondary efficacy endpoint analyses demonstrated clinically meaningful benefit in terms of decreased need for rescue treatment (14% of patients on Promacta compared to 59% of patients on placebo).

PETIT2 was a Phase III, multi-center, two-part study to investigate the efficacy, safety and tolerability of Promacta in pediatric patients with previously treated chronic ITP. Part 1 was randomized, double-blind and placebo-controlled and Part 2 was an open-label extension. The primary endpoint, which was percentage of participants who achieved a platelet count >=50 Gi/L without rescue therapy for at least six out of eight weeks between Weeks 5 and 12 of Part 1 of the study, was met by 43% of patients treated with Promacta and 4% of patients treated with placebo (p=0.0011). This result was consistent across the age cohorts. The secondary efficacy endpoint analyses demonstrated clinically meaningful benefit in terms of decreased need for rescue treatment (18% of patients on Promacta compared to 22% of patients on placebo), and reduction or discontinuation of baseline ITP medications (50% or 5/10 patients in the open-label phase who were receiving other ITP therapy at baseline) over the randomized and Promacta-only treatment periods.
In both studies, safety was consistent with the known safety profile of Promacta in chronic ITP in adults and the population under study. No new safety signals were detected. The most common adverse reactions in pediatric chronic ITP patients six years and older (greater than or equal to 10% and greater than placebo) were upper respiratory tract infection, nasopharyngitis and rhinitis.

**DEFINITIONS**

Idiopathic: The cause is unknown.

Thrombocytopenia: A decreased number of platelets in the blood.

Purpura: The purple discoloring of the skin, as with a bruise.

Immune thrombocytopenia: A bleeding disorder where the blood is unable to clot, as a result of a low number of platelets or thrombocytes.

**APPENDIX**

**Appendix 1: Causes of Secondary Immune Thrombocytopenia**

<table>
<thead>
<tr>
<th>Causes of Secondary Immune Thrombocytopenia</th>
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<tbody>
<tr>
<td>• Antiphospholipid syndrome</td>
<td>• Infection</td>
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<td>• Autoimmune thrombocytopenia</td>
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<tr>
<td>• Common variable immune deficiency</td>
<td>– <em>Helicobacter pylori</em></td>
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<td>• Drug-induced</td>
<td>– Hepatitis C</td>
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<tr>
<td>• Lymphoproliferative disorders</td>
<td>– Human immunodeficiency virus</td>
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<tr>
<td>• Post bone marrow transplantation</td>
<td>– Varicella zoster</td>
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<td>• Post vaccination</td>
<td>• Systemic lupus erythematosus</td>
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**Appendix 2: Dose Adjustments of Promacta for Chronic ITP²**

Monitoring and Dose Adjustment: After initiating Promacta, adjust the dose to achieve and maintain a platelet count greater than or equal to 50 x 10⁹/L as necessary to reduce the risk for bleeding. Do not exceed a dose of 75 mg daily.

Monitor clinical hematology and liver tests regularly throughout therapy with Promacta and modify the dosage regimen of Promacta based on platelet counts as outlined in the following table:

<table>
<thead>
<tr>
<th>Platelet Count Result</th>
<th>Dose Adjustment or Response</th>
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<tr>
<td>&lt;50 x 10⁹/L following at least 2 weeks of PROMACTA</td>
<td>Increase daily dose by 25 mg to a maximum of 75 mg/day.</td>
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<td>For patients taking 12.5 mg once daily, increase the dose to 25 mg daily before increasing the dose amount by 25 mg.</td>
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</table>
≥200 x 10⁹/L to ≤400 x 10⁹/L at any time

Decrease the daily dose by 25 mg. 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.

>400 x 10⁹/L

Stop PROMACTA; increase the frequency of platelet monitoring to twice weekly.

Once the platelet count is <150 x 10⁹/L, 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.

>400 x 10⁹/L after 2 weeks of therapy at lowest dose of PROMACTA

Discontinue PROMACTA.

During therapy with Promacta, assess CBCs with differentials, including platelet counts, weekly until a stable platelet count has been achieved. Obtain CBCs with differentials, including platelet counts, monthly thereafter.

When switching between the oral suspension and tablet, assess platelet counts weekly for 2 weeks, and then follow standard monthly monitoring.

In patients with ITP and hepatic impairment (Child-Pugh Class A, B, C), after initiating PROMACTA or after any subsequent dosing increase, wait 3 weeks before increasing the dose.

Modify the dosage regimen of concomitant ITP medications, as medically appropriate, to avoid excessive increases in platelet counts during therapy with Promacta. Do not administer more than one dose of PROMACTA within any 24-hour period.

Discontinuation: Discontinue Promacta if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of therapy with Promacta at the maximum daily dose of 75 mg. Excessive platelet count responses, as outlined in Table 1, or important liver test abnormalities also necessitate discontinuation of Promacta. Obtain CBCs with differentials, including platelet counts, weekly for at least 4 weeks following discontinuation of Promacta.

**CODING INFORMATION:** THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

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REFERENCES

**Package Insert, FDA, Drug Compendia**


**Clinical Trials, Definitions, Peer-Reviewed Publications**


**Government Agencies, Professional Societies, and Other Authoritative Publications**