Clinical Policy: Eltrombopag (Promacta)

Reference Number: ERX.SPA.71
Effective Date: 10.01.16
Last Review Date: 02.22
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Eltrombopag (Promacta®) is a thrombopoietin receptor agonist.

FDA Approved Indication(s)
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.
- Thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. 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.
- In combination with standard immunosuppressive therapy for the first-line treatment of adults and pediatric patients 2 years and older with severe aplastic anemia.
- Patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.

Limitation(s) 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.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results, or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Promacta is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Persistent/Chronic Immune Thrombocytopenia (must meet all)**:**

1. Diagnosis of persistent or chronic ITP (*see Appendix D*);
2. Prescribed by or in consultation with a hematologist;
3. Age ≥ 1 year;
4. Current (within 30 days) platelet count is < 30,000/µL or member has an active bleed;
5. Member must meet one of the following (a or b):
   a. Failure of a systemic corticosteroid;
   b. Member has intolerance or contraindication to systemic corticosteroids, and failure of an immune globulin, unless contraindicated or clinically significant adverse effects are experienced (*see Appendix B*);

   **Prior authorization may be required for immune globulins*

6. Promacta is not prescribed concurrently with rituximab or another thrombopoietin receptor agonist (e.g., Doptelet®, Nplate®);
7. Dose does not exceed 75 mg (1 tablet) per day.

Approval duration: 6 months

B. Chronic Hepatitis C-Associated Thrombocytopenia (must meet all)**:**

1. Diagnosis of chronic hepatitis C-associated thrombocytopenia;
2. Prescribed by or in consultation with a hematologist, hepatologist, gastroenterologist, or infectious disease specialist;
3. Age ≥ 18 years;
4. Promacta will be used concomitantly with interferon-based therapy;
5. The degree of thrombocytopenia has prevented the initiation of interferon-based therapy or limited the ability to maintain interferon-based therapy;
6. Current (within 30 days) platelet count is < 75,000/µL;
7. Dose does not exceed 100 mg (2 tablets) per day.

Approval duration: 6 months

C. Severe Aplastic Anemia (must meet all)**:**

1. Diagnosis of severe aplastic anemia;
2. Prescribed by or in consultation with a hematologist;
3. Age ≥ 2 years;
4. Promacta is prescribed for one of the following (a or b):
   a. As first-line therapy in combination with immunosuppressive therapy (e.g., Atgam®, cyclosporine, cyclophosphamide);
   b. Refractory or second-line treatment as a single agent following insufficient response to immunosuppressive therapy (e.g., Atgam, cyclosporine, cyclophosphamide);

   **Prior authorization may be required for Atgam*
5. Current (within 30 days) platelet count is < 50,000/µL;
6. Dose does not exceed 150 mg (2 tablets) per day.

Approval duration: 6 months

D. Myelodysplastic Syndromes (off-label) (must meet all)**:**

1. Diagnosis of myelodysplastic syndromes (MDS);
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Member has lower-risk MDS (IPSS-R [Very Low, Low, Intermediate]);
4. One of the following (a or b):
   a. Member has severe or refractory thrombocytopenia following disease progression or no response to hypomethylating agents (e.g., azacitadine, decitabine), immunosuppressive therapy (e.g., Atgam®, cyclosporine), or clinical trial;
   b. Member has thrombocytopenia or neutropenia and one of the following (i, ii, iii, or iv):
      i. Age ≤ 60 years with ≤ 5% marrow blasts;
      ii. Hypocellular marrows;
      iii. Paroxysmal nocturnal hemoglobinuria (PNH) clone positivity;
      iv. *STAT-3* mutant cytotoxic T-cell clones;
5. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).*

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 6 months

E. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Persistent/Chronic Immune Thrombocytopenia, Chronic Hepatitis C-Associated Thrombocytopenia and Severe Aplastic Anemia (must meet all)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy (*see Appendix D*);
3. Current (within the last 90 days) platelet count is < 400,000/µL;
4. For chronic hepatitis C-associated thrombocytopenia, member continues to receive interferon-based therapy;
5. For persistent or chronic ITP: Promacta is not prescribed concurrently with rituximab or another thrombopoietin receptor agonist (e.g., Doptelet, Nplate);
6. If request is for a dose increase, new dose does not exceed the following:
   a. Persistent or chronic ITP: 75 mg (1 tablet) per day;
   b. Chronic hepatitis C-associated thrombocytopenia: 100 mg (2 tablets) per day;
   c. Severe aplastic anemia: 150 mg (2 tablets) per day.

Approval duration:
Hepatitis C-associated thrombocytopenia: 6 months
All other indications: 12 months

B. Myelodysplastic Syndromes (off-label) (must meet all)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions, or documentation supports that member is currently receiving Promacta for MDS and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).*
   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 12 months

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ANC: absolute neutrophil count
FDA: Food and Drug Administration
IPSS-R: Revised International Prognostic Scoring System
ITP: chronic immune thrombocytopenia
MDS: myelodysplastic syndromes
PNH: paroxysmal nocturnal hemoglobinuria
STAT-3: signal transducer and activator of transcription

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Corticosteroids*		
dexamethasone	**ITP** Oral dosage: *Adults*: Initially, 0.75 to 9 mg/day PO, given in 2 to 4 divided doses. Adjust according to patient response. *Children and adolescents*: 0.02 to 0.3 mg/kg/day PO or 0.6 to 9 mg/m^2/day PO, given in 3 to 4 divided doses Intramuscular or intravenous dosage: *Adults:* Initially, 0.5 to 9 mg/day IV or IM, given in 2 to 4 divided doses. Adjust according to patient response. *Children:* 0.02 to 0.3 mg/kg/day or 0.6 to 9 mg/m^2/day IV or IM given in 3 or 4 divided doses. Adjust according to patient response.	Dosage must be individualized and is highly variable depending on the nature and severity of the disease, route of treatment, and on patient response.
methylprednisolone	**ITP** Oral dosage: *Adults:* 4 to 48 mg/day PO in 4 divided doses. Adjust according to patient response. *Children:* 0.5 to 1.7 mg/kg/day PO in divided doses every 6 to 12 hrs Intravenous dosage: *Adults:* 10 to 40 mg IV every 4 to 6 hours for up to 72 hours *Children:* 0.11 to 1.6 mg/kg/day IV in 3 or 4 divided doses.	Dosage must be individualized and is highly variable depending on the nature and severity of the disease, route of treatment, and on patient response.
prednisone	**ITP** *Adults:* Initially, 1 mg/kg PO once daily; however, lower doses of 5 mg/day to 10 mg/day PO are preferable for long-term treatment.	Dosage must be individualized and is highly variable depending on the nature and severity of the disease, route of treatment, and on patient response.
Immune globulins		
immune globulins (e.g., Carimune® NF, Flebogamma® DIF 10%, Gammagard® S/D, Gammaked™, Gamunex®-C, Gammaplex®, Octagam® 10%, Privigen®)	**ITP** Refer to prescribing information	Refer to prescribing information
Immunosuppressive agents*		
Atgam® (antithymocyte globulin)	**Aplastic anemia** 10 to 20 mg/kg/day IV infusion for 8 to 14 days, continuing with every-other-day dosing up to a total of 21 doses, if needed	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Off-label dosing: 40 mg/kg daily for four consecutive days in combination with cyclosporine	
cyclosporine† (Sandimmune®)	**Aplastic anemia** 12 mg/kg PO daily	Varies
cyclophosphamide†	**Aplastic anemia** 45 to 50 mg/kg IV divided over 4 days	Varies

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
**Examples of corticosteroids/immunosuppressive agents provided are not all inclusive*
† Off-label indication

Appendix C: Contraindications/Boxed Warnings
- Contraindication(s): none reported
- Boxed warning(s): In patients with chronic hepatitis C, Promacta in combination with interferon and ribavirin may increase the risk of hepatic decompensation. Promacta may increase the risk of severe and potentially life threatening hepatotoxicity. Monitor hepatic function and discontinue dosing as recommended.

Appendix D: General Information
- Definition of persistent vs chronic ITP per the 2019 American Society of Hematology Guideline
  - Persistent ITP: ITP duration of 3-12 months
  - Chronic ITP: ITP duration of > 12 months
- Examples of positive response to therapy may include:
  - For ITP or hepatitis C-associated thrombocytopenia:
    - Increase in platelet count from baseline levels;
    - Platelet count ≥ 50,000/µL;
    - Reduction in clinically important bleeding events;
  - For aplastic anemia: any of the following hematologic responses:
    - Platelet count ≥ 50,000/µL
    - Platelet count increases to 20,000/µL above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks;
    - Hemoglobin increase > 1.5 g/dL, or a reduction of ≥ 4 units of red blood cell (RBC) transfusions for 8 consecutive weeks;
    - Absolute neutrophil count (ANC) increase of 100% or an ANC increase greater than 500/µL.
- MDS prognostic scoring system online calculator for IPSS-R: https://qxmd.com/calculate/calculator_109/mds-revised-international-prognostic-scoring-system-ipss-r

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Persistent or chronic ITP	Adults and pediatrics age ≥ 6 years: 50 mg PO QD Pediatrics age 1 to 5 years: 25 mg PO QD Dose reductions are needed for patients with hepatic impairment and some patients of East Asian ancestry. Adjust to maintain platelet count ≥ 50,000/µL.	75 mg/day
Chronic hepatitis C-associated thrombocytopenia	25 mg PO QD Adjust to achieve target platelet count required to initiate antiviral therapy.	100 mg/day

Indication	Dosing Regimen	Maximum Dose
Severe aplastic anemia	After an insufficient response to immunosuppressive therapy: 50 mg PO QD Reduce initial dose in patients with hepatic impairment or patients of East Asian ancestry. Adjust to maintain platelet count greater than 50,000/µL. For first-line treatment in combination with immunosuppressive therapy: Patients 12 years and older: 150 mg PO QD Patients 6 to 11 years: 75 mg PO QD Patients 2 to 5 years: 2.5 mg/kg PO QD Reduce initial dose in patients with hepatic impairment or patients of East Asian ancestry. Adjust to maintain platelet count greater than 50,000/µL. Total duration of treatment is 6 months.	150 mg/day

VI. Product Availability

- Tablets: 12.5 mg, 25 mg, 50 mg, 75 mg
- Oral suspension: 12.5 mg, 25 mg

VII. References

1. Promacta Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; October 2021. Available at: https://www.us.promacta.com/. Accessed November 15, 2021.
2. Townsley DM, et al. Eltrombopag added to standard immunosuppression for aplastic anemia. N Engl J of Med. Apr 2017;376(16):1540-1550.
3. Killick SB, et al. Guidelines for the diagnosis and management of adult aplastic anemia. British Journal of Haematology, 2016, 172, 187-207.
4. Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011; 117(16): 4190-4207.
5. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc. Updated periodically. Accessed November 15, 2021.
6. National Comprehensive Cancer Network. Myelodysplastic Syndromes Version 2.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf. Accessed November 15, 2021.
7. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed November 15, 2021.
8. Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv (2019) 3 (23): 3829–3866.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q18 annual review: No significant changes. References reviewed and updated.	11.14.17	02.18
Chronic ITP: removed requirement related to splenectomy based on specialist feedback.	08.20.18	11.18
1Q 2019 annual review: no significant changes; updated limitations of use per package insert; added requirement that initial platelet counts be current (within 30 days) for all indications; for cont tx approval, clarified that member must be continuing on interferon-based therapy; added MDS as a diagnosis not covered per package insert; references reviewed and updated.	10.30.18	02.19

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Criteria added for new FDA indication: first-line treatment of aplastic anemia in combination with standard immunosuppressive therapy; added oral suspension formulation; references reviewed and updated.	01.15.19	05.19
1Q 2020 annual review: removed MDS from Section III and added MDS criteria set as NCCN supported category 2A recommendation for use; revised systemic corticosteroid *and* immune globulin trial to tiered re-direction with immune globulin trial only if corticosteroid cannot be used to align with Nplate criteria, ASH 2011 guideline and specialist feedback; references reviewed and updated.	01.14.20	02.20
Added requirement that Promacta is not prescribed concurrently with rituximab or another thrombopoietin receptor agonist for ITP.	05.19.20	08.20
1Q 2021 annual review: for aplastic anemia clarified use either as first-line combination therapy or second-line as monotherapy, removed upper age limit for combination therapy per clinical trial baseline characteristics of study population; references reviewed and updated.	11.17.20	02.21
RT4: updated criteria in response to FDA label revision to include persistent or chronic ITP	02.23.21	
1Q 2022 annual review: clarified definition of persistent vs chronic ITP in Appendix D per 2019 ASH guideline; for MDS removed IPSS and WPSS risk categorizations as IPSS-R is preferred per NCCN; included criteria for specific circumstances for MDS where disease progression on other agents is not necessary per NCCN; references reviewed and updated.	11.15.21	02.22

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.