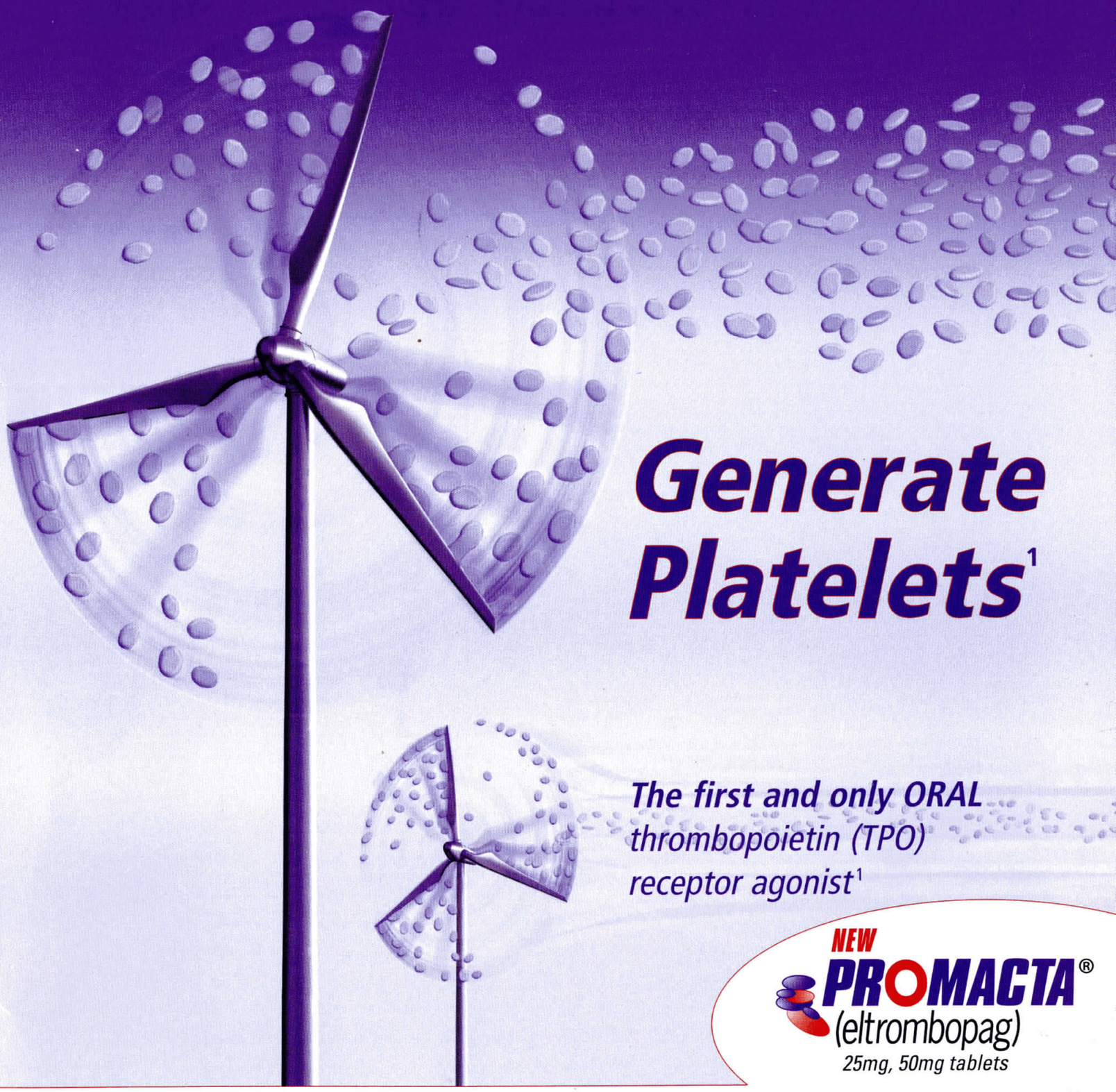
When corticosteroids are not enough for your patients[1]



Generate Platelets[1]

The first and only ORAL thrombopoietin (TPO) receptor agonist[1]

NEW

PROMACTA®

(eltrombopag)

25mg, 50mg tablets

PROMACTA is indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (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 increases the risk for bleeding. PROMACTA should not be used in an attempt to normalize platelet counts.[1]

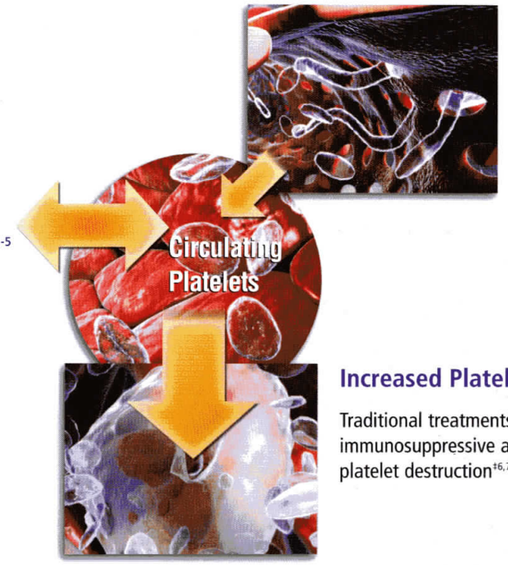
BOXED WARNING

PROMACTA may cause hepatotoxicity. Patients receiving therapy with PROMACTA must have regular monitoring of serum liver tests (*see Laboratory Monitoring*). Discontinue PROMACTA if ALT levels increase to ≥3X upper limit of normal (ULN) and are: progressive; or persistent for ≥4 weeks, or; accompanied by increased direct bilirubin; or accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation. Reinitiating treatment with PROMACTA is not recommended and should be considered only with close medical supervision and under exceptional circumstances where the potential benefit outweighs the risk.

Because of the risk for hepatotoxicity and other risks, PROMACTA is available only through a restricted distribution program called PROMACTA *Cares*. Under the PROMACTA *CARES* Program, only prescribers, pharmacies, and patients registered with the program are able to prescribe, dispense, and receive PROMACTA. To enroll in the PROMACTA *CARES* Program, call 1-877-9-PROMACTA.

ITP: an out-of-balancing act for blood platelets

Platelet destruction is only part of the problem[2-5]



Decreased Platelet Production*

Increased destruction and decreased production of platelets result in an imbalance[2-5]

Platelet Splenic Sequestration†[2-5]

Increased Platelet Destruction‡

Traditional treatments such as steroids and immunosuppressive agents address only platelet destruction[†6,7]

Normally, TPO regulates platelets in the body[2,8-12]

- In healthy people, if there is a drop in platelets due to injury or other causes, more circulating TPO becomes available[2,8-12]
- In patients with ITP, there is no compensatory increase in TPO synthesis to stimulate platelet production[2,8-12]

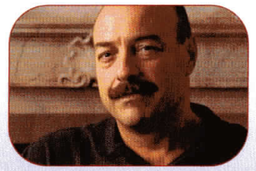
Nonpeptide TPO receptor agonists, a novel approach to ITP, produce platelets by stimulating megakaryocyte precursor proliferation and differentiation[6,13]

*Megakaryocyte extending proplatelets into bone marrow sinusoids and releasing platelets.
†Platelets moving into the spleen.
‡Macrophages engulfing and digesting platelets.

Please see accompanying full Prescribing Information, including BOXED WARNING.

Generate Platelets[1]

PROMACTA is beneficial for ITP therapy[1,7]



Henry, age 48

- *Long-standing history of ITP*
- *Working professional*
- *Insufficient response to corticosteroids: platelet counts have remained <30,000/mcL while on corticosteroids*
- *Wants to raise and maintain platelet counts above 50,000/mcL*

Grace, age 36

- *History of chronic ITP with platelet count between 18,000/mcL and 30,000/mcL with intermittent oral mucosal bleeding*
- *Failed to respond to corticosteroids*
- *Had URI symptoms and developed reddish, punctate lesions on her lower extremities and blood-tinged nasal drainage*
- *Platelet count has dropped to 10,000/mcL*

Luisa, age 50

- *Platelet count between 5000/mcL and 10,000/mcL with chronic petechiae and intermittent oral mucosal bleeding*
- *Relapse following corticosteroids and splenectomy*
- *Wants to receive maintenance therapy to increase platelet counts and avoid bleeding*

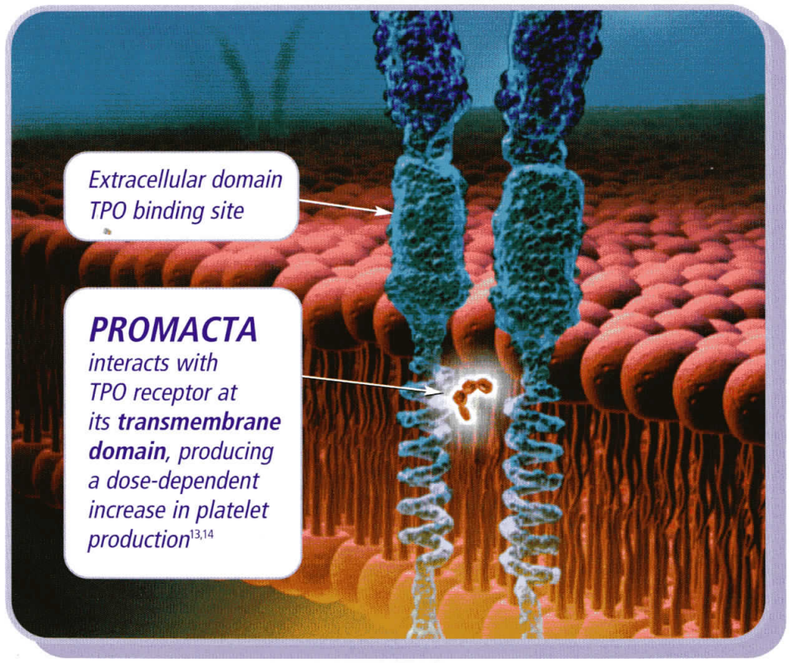
Additional Safety Information Regarding Risk of Hepatotoxicity: Reinitiating treatment with PROMACTA is not recommended. If the potential benefit for reinitiating PROMACTA treatment is considered to outweigh the risk for hepatotoxicity, then cautiously reintroduce PROMACTA and measure serum liver tests weekly during the dose adjustment phase. If liver test abnormalities persist, worsen or recur, then permanently discontinue PROMACTA. Exercise caution when administering PROMACTA to patients with hepatic disease. Use a lower starting dose of PROMACTA in patients with moderate to severe hepatic disease and monitor closely.

NEW
PROMACTA® (eltrombopag)
25mg, 50mg tablets

Introducing PROMACTA—

The first and only **ORAL** TPO receptor agonist to increase platelet production for the treatment of chronic ITP[1]

PROMACTA is indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (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 increases the risk for bleeding. PROMACTA should not be used in an attempt to normalize platelet counts.[1]



PROMACTA is a nonpeptide TPO receptor agonist that[1,13]:

- Induces an intracellular signal
- Triggers the proliferation and differentiation of megakaryocyte precursors
- Increases platelet production

PROMACTA is not a corticosteroid and is not an immunosuppressant

Bone Marrow Reticulin Formation and Risk for Bone Marrow Fibrosis: PROMACTA is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists increase the risk for development or progression of reticulin fibers within the bone marrow. Prior to initiation of PROMACTA, examine the peripheral blood smear closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of PROMACTA, perform CBC with WBC differential monthly. If the patient develops new or worsening morphological abnormalities or cytopenia(s), discontinue treatment with PROMACTA and consider a bone marrow biopsy, including staining for fibrosis.

Please see accompanying full Prescribing Information, including BOXED WARNING.

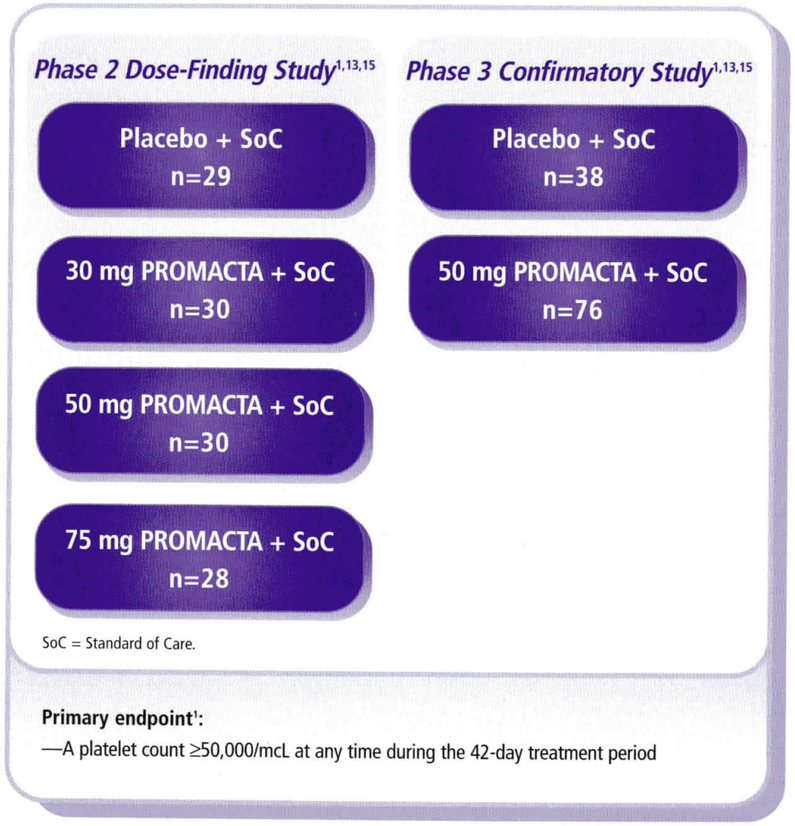
Placebo-controlled Phase 2 and Phase 3 study design[1]

In both studies, patients with baseline platelet counts <30,000/mcL were randomized and stratified by[1]:

—Splenectomy status

—Use of concomitant ITP therapy

—Platelet count <15,000/mcL

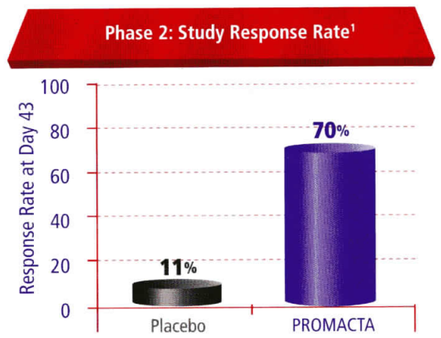


SoC = Standard of Care.

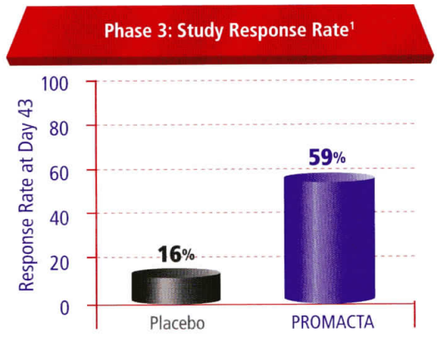
Primary endpoint[1]:

—A platelet count ≥50,000/mcL at any time during the 42-day treatment period

In chronic ITP, PROMACTA boosts platelet counts to levels ≥50,000/mcL[1,7]



P<0.001 for PROMACTA versus placebo



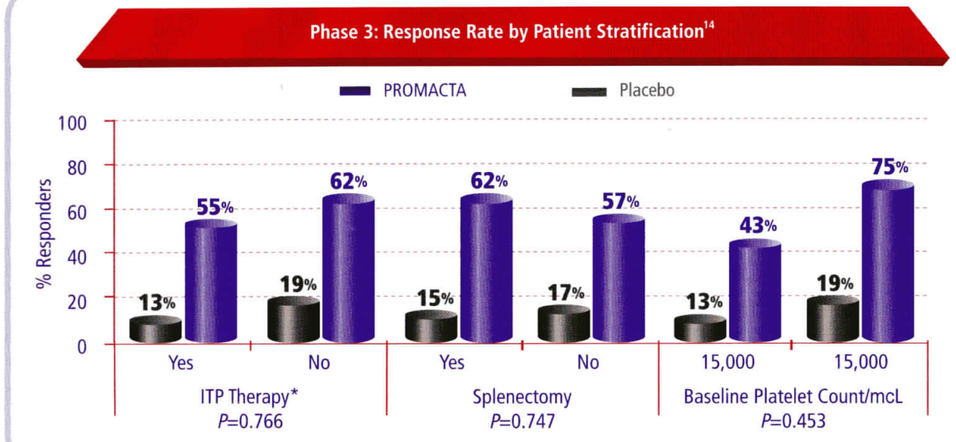
P<0.001 for PROMACTA versus placebo

- Phase 2: 70% of patients on 50 mg PROMACTA achieved platelet counts ≥50,000/mcL by Day 43, compared with 11% for placebo (*P*<0.001)
- Phase 3: 59% of patients achieved platelet counts ≥50,000/mcL by Day 43, compared with 16% for placebo (*P*<0.001)[1]
- In general, increases in platelet counts were detected 1 week following initiation of PROMACTA, and the maximum response was observed after 2 weeks of therapy; platelet counts generally decreased within 1 to 2 weeks after discontinuing PROMACTA[1]

Worsened Thrombocytopenia and Hemorrhage Risk After PROMACTA Cessation: Discontinuation of PROMACTA may result in thrombocytopenia of greater severity than was present prior to therapy with PROMACTA. This worsened thrombocytopenia may increase the patient's risk of bleeding, particularly if PROMACTA is discontinued while the patient is on anticoagulants or antiplatelet agents. In the controlled clinical studies, transient decreases in platelet counts to levels lower than baseline were observed following discontinuation of treatment in 10% and 6% of the PROMACTA and placebo groups, respectively. Serious hemorrhagic events requiring the use of supportive ITP medications occurred in 3 severely thrombocytopenic patients within one month following the discontinuation of PROMACTA; none were reported among the placebo group. Following discontinuation of PROMACTA, obtain weekly CBCs, including platelet counts for at least 4 weeks and consider alternative treatments for worsening thrombocytopenia, according to current treatment guidelines.

Please see accompanying full Prescribing Information, including BOXED WARNING.

PROMACTA demonstrates a consistent response across chronic ITP patient types[1,15]



*ITP therapy includes prednisone, dexamethasone, prednisolone, methylprednisolone, deflazacort, corticosteroids (not otherwise specified), and hydrocortisone.[15]

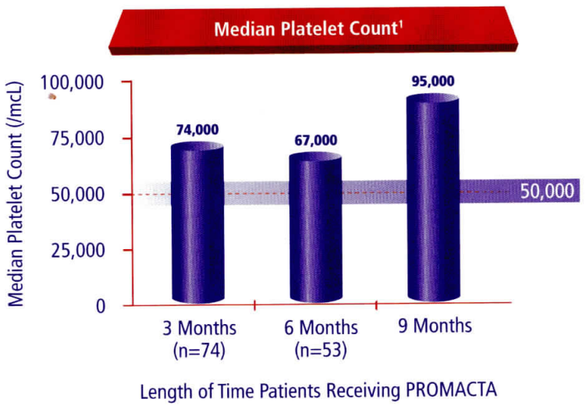
- PROMACTA was effective in getting platelet counts to ≥50,000/mcL in the majority of patients, regardless of concomitant ITP therapy or splenectomy status by Day 43[15]
- Responders are those patients who achieve platelet counts of ≥50,000/mcL at any time during the treatment period
- An increase in platelet counts to >200,000/mcL occurred in 3% and 25% of the patients in the placebo and PROMACTA groups, respectively. Study drug was discontinued in these subjects and they were considered responders

Thrombotic/Thromboembolic Complications: Thrombotic/thromboembolic complications may result from excessive increases in platelet counts. Excessive doses of PROMACTA or medication errors that result in excessive doses of PROMACTA may increase platelet counts to a level that produces thrombotic/thromboembolic complications. In the controlled clinical studies, one thrombotic/thromboembolic complication was reported within the group that received PROMACTA and none within the placebo group. Seven patients experienced thrombotic/thromboembolic complications in the extension study. Use caution when administering PROMACTA to patients with known risk factors for thromboembolism. 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 a platelet count of ≥50 x 10^9/L.

PROMACTA, in an extension study, demonstrated a similar side-effects profile to the placebo-controlled studies[1]

- Patients who completed any prior clinical study with PROMACTA were enrolled in an open-label, single-arm study
- Primary objective: evaluate the safety and tolerability of PROMACTA over a long-term treatment period
- Attempts were made to decrease dose or eliminate the need for concomitant ITP medications while on PROMACTA

Extension study



- Median baseline count = 18,000/mcL
- Median daily dose following 6 months of treatment was 50 mg

Malignancies and Progression of Malignancies: Stimulation of the TPO receptor on the surface of hematopoietic cells may increase the risk for hematologic malignancies. PROMACTA is not indicated for the treatment of thrombocytopenia due to causes of thrombocytopenia (eg, myelodysplasia or chemotherapy) other than chronic ITP.

Cataracts: In the controlled clinical studies, cataracts developed or worsened in five patients (5%) who received 50 mg PROMACTA daily and two placebo-group patients (3%). In the extension study, cataracts developed or worsened in 4% of patients who underwent ocular examination prior to therapy with PROMACTA. Cataracts were observed in toxicology studies of eltrombopag in rodents. Perform a baseline ocular examination prior to administration of PROMACTA and, during therapy with PROMACTA, regularly monitor patients for signs and symptoms of cataracts.

Please see accompanying full Prescribing Information, including BOXED WARNING.

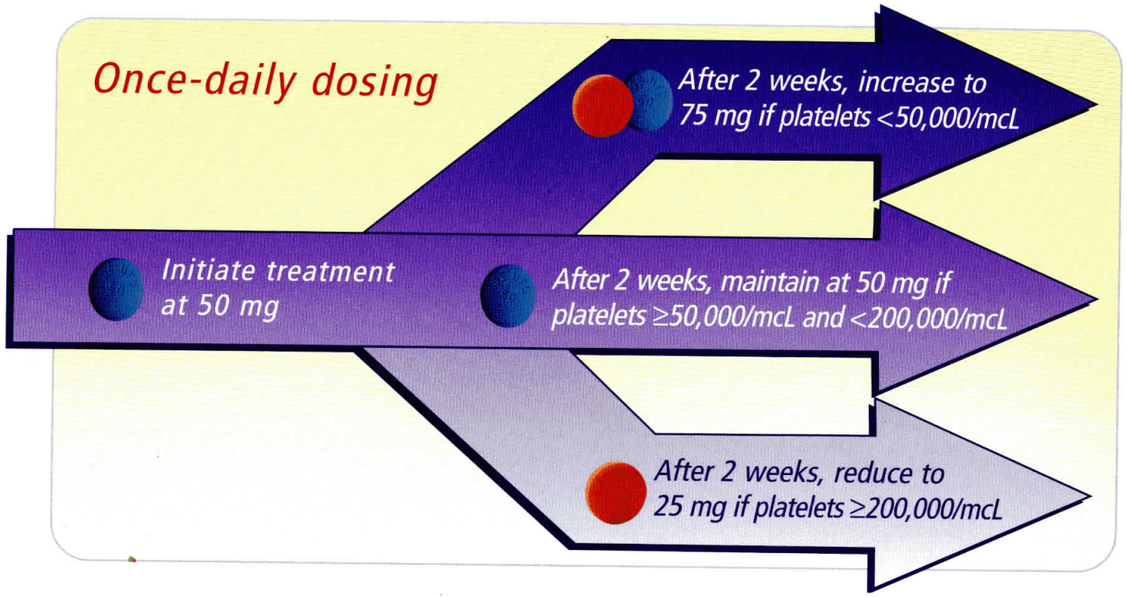
PROMACTA: tolerability profile in controlled clinical trials[1]

Adverse Reactions Identified in Two Placebo-Controlled Studies

	PROMACTA 50 mg N=106 (%)	Placebo N=67 (%)
Nausea	6	4
Vomiting	4	3
Menorrhagia	4	1
Myalgia	3	1
Paresthesia	3	1
Cataract	3	1
Dyspepsia	2	0
Ecchymosis	2	1
Thrombocytopenia	2	0
Increased ALT	2	0
Increased AST	2	0
Conjunctival hemorrhage	2	1

The table presents the most common adverse drug reactions experienced by more than one patient receiving PROMACTA from the placebo-controlled studies with a higher instance in PROMACTA versus placebo.

PROMACTA offers once-daily ORAL dosing[1]



- Initiate PROMACTA at a reduced dose of 25 mg once daily for patients of East Asian ancestry such as Chinese, Japanese, Taiwanese, or Korean
- Initiate PROMACTA at a reduced dose of 25 mg once daily for patients with moderate or severe hepatic impairment
- The maximum dose of PROMACTA is 75 mg per day. Do not administer more than 1 dose of PROMACTA within any 24-hour period
- If bilirubin is elevated, perform fractionation
- If the platelet count is >400,000/mcL after two weeks of therapy at the lowest dose, the prescriber should permanently discontinue PROMACTA
- 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 of the Prescribing Information, or important liver test abnormalities also necessitate discontinuation of PROMACTA

Considerations[1]

Take PROMACTA on an empty stomach (1 hour before or 2 hours after a meal). Allow at least a 4-hour interval between PROMACTA and other medications (eg, antacids), calcium-rich foods (eg, dairy products and calcium fortified juices), or supplements containing polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, and zinc.

Dose adjustments of PROMACTA

Platelet Counts	Dose Adjustments by 25-mg Increments
<50,000/mcL following at least 2 weeks of PROMACTA	■ Increase daily dose by 25 mg up to a maximum of 75 mg/day
200,000-400,000/mcL	■ Decrease daily dose by 25 mg *Wait 2 weeks to assess the effects of this and any subsequent dose adjustments*
>400,000/mcL	■ Stop PROMACTA ■ Monitor platelets twice weekly ■ Reinitiate therapy at a daily dose reduced by 25 mg once the platelet count is <150,000/mcL
>400,000/mcL after two weeks of therapy at lowest dose of PROMACTA	■ Permanently discontinue PROMACTA

- Modify the dosage regimen of concomitant ITP medications, as medically appropriate, to avoid excessive increases in platelet counts during therapy with PROMACTA
- Use the lowest dose of PROMACTA to achieve and maintain a platelet count of ≥50,000/mcL as necessary to reduce the risk of bleeding

Laboratory Monitoring

Complete Blood Counts (CBCs): Monitor CBCs, including platelet counts and WBC differentials prior to initiation, throughout, and following discontinuation of PROMACTA therapy. Prior to the initiation of PROMACTA, examine the peripheral blood differential to establish the extent of red and white blood cell abnormalities. Obtain CBCs, including platelet counts and peripheral blood smears, weekly during the dose adjustment phase of therapy with PROMACTA and then monthly following establishment of a stable dose of PROMACTA. Obtain CBCs, including platelet counts, weekly for at least 4 weeks following discontinuation of PROMACTA.

Liver Tests: Monitor serum liver tests (ALT, AST, total and fractionated bilirubin) prior to initiation of PROMACTA, every 2 weeks during the dose adjustment phase, and monthly following establishment of a stable dose. If abnormal levels are detected, repeat the tests within 3 to 5 days. If the abnormalities are confirmed, monitor serum liver tests weekly until the abnormality(ies) resolve, stabilize, or return to baseline levels. Discontinue PROMACTA for the development of clinically important liver test abnormalities.

For more details, please see Dosage and Administration section of full Prescribing Information.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROMACTA safely and effectively. See full prescribing information for PROMACTA.

PROMACTA® (eltrombopag) Tablets
For oral use
Initial U.S. Approval: 2008

WARNING: RISK FOR HEPATOTOXICITY
See full prescribing information for complete boxed warning
PROMACTA may cause hepatotoxicity:
- **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. 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 the abnormality(ies) resolve, stabilize, or return to baseline levels.**
- **Discontinue PROMACTA if ALT levels increase to ≥3X upper limit of normal (ULN) and are:**
  - **progressive, or**
  - **persistent for ≥4 weeks, or**
  - **accompanied by increased direct bilirubin, or**
  - **accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation.**

---------- INDICATIONS AND USAGE ----------

PROMACTA is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura 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. PROMACTA should not be used in an attempt to normalize platelet counts. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- The starting dose of PROMACTA is 50 mg once daily for most patients; for patients of East Asian ancestry or patients with moderate or severe hepatic insufficiency, the starting dose is 25 mg once daily. (2)
- Give on an empty stomach (1 hour before or 2 hours after a meal). (2)
- [illegible] PROMACTA [illegible]

---------- CONTRAINDICATIONS ----------

None. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- PROMACTA may cause hepatotoxicity. Increases in serum aminotransferase levels and bilirubin were observed. Liver chemistries must be measured before the initiation of treatment and regularly during treatment. (5.1)
- Exercise caution when administering to patients with hepatic impairment. (5.1, 8.6)
- PROMACTA is a thrombopoietin receptor agonist and TPO-receptor agonists increase the risk for development or progression of reticulin fiber deposition within the bone marrow. Monitor peripheral blood for signs of marrow fibrosis. (5.2)
- Discontinuation may result in worsened thrombocytopenia than was present prior to therapy. Monitor weekly complete blood counts (CBCs), including platelet counts for at least 4 weeks after discontinuation. (5.3)
- Excessive doses of PROMACTA may increase platelet counts to a level that produces thrombotic/thromboembolic complications. (5.4)
- PROMACTA may increase the risk for hematological malignancies, especially in patients with myelodysplastic syndrome. (5.5)
- Monitor CBCs, including platelet counts and peripheral blood smears, weekly during the dose adjustment phase of therapy with PROMACTA and then monthly following establishment of a stable dose of PROMACTA. (5.6)
- Because of the risk for hepatotoxicity and other risks, PROMACTA is available only through a restricted distribution program. To enroll in the restricted distribution program, PROMACTA *CARES*, call 1-877-9-PROMACTA. (5.8)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions (occurring in more than 1 patient receiving PROMACTA and at a higher rate in PROMACTA versus placebo) were: nausea, vomiting, menorrhagia, myalgia, paresthesia, cataract, dyspepsia, ecchymosis, thrombocytopenia, increased ALT/AST and conjunctival hemorrhage. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

- Eltrombopag is an inhibitor of OATP1B1 transporter. Monitor patients closely for signs and symptoms of excessive exposure to the drugs that are substrates of OATP1B1 (e.g., rosuvastatin) and consider reduction of the dose of these drugs. (7.2)
- Polyvalent cations (e.g., iron, calcium, aluminum, magnesium, selenium, and zinc) significantly reduce the absorption of eltrombopag; PROMACTA must not be taken within 4 hours of any medications or products containing polyvalent cations such

ices
MACTA [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2008. **2.** Cines DB, Blanchette VS. Immune thrombocytopenic purpura. *N Engl J Med.* 2002;346(13):995-1008.
sheimer T. Pathophysiology and thrombokinetics in autoimmune thrombocytopenia. *Blood Rev.* 2002;16(1):7-8. **4.** Houwerzijl EJ, Blom NR, van der Want JJL, et al. Ultrastructural study morphologic features of apoptosis and para-apoptosis in megakaryocytes from patients with idiopathic thrombocytopenic purpura. *Blood.* 2004;103(2):500-506. **5.** Cines DB, McMillan R. ment of adult idiopathic thrombocytopenic purpura. *Annu Rev Med.* 2005;56:425-442. **6.** Stasi R, Evangelista ML, Stipa E, Buccisano F, Venditti A, Amadori S. Idiopathic ocytopenic purpura: current concepts in pathophysiology and management. *Thromb Haemost.* 2008;991:4-13. **7.** Cines DB, Bussel JB. How I treat idiopathic thrombocytopenic purpura *lood.* 2005;106(7):2244-2251. **8.** Kaushansky K. Lineage-specific hematopoietic growth factors. *N Engl J Med.* 2006;354(19):2034-2045. **9.** Kaushansky K. Thrombopoietin: a tool for anding thrombopoiesis. *J Thromb Haemost.* 2003;1(7):1587-1592. **10.** Kato T, Matsumoto A, Ogami K, Tahara T, Morita H, Miyazaki H. Native thrombopoietin: structure and function. *ells.* 1998;16(5):322-328. **11.** Aledort LM, Hayward CPM, Chen MG, Nichol JL, Bussel JB, for the ITP Study Group. Prospective screening of 205 patients with ITP, including is, serological markers, and the relationship between platelet counts, endogenous thrombopoietin, and circulating antithrombopoietin antibodies. *Am J Hematol.* 2004;76(3):205-213. kson-Miller CL, DeLorme E, Tian SS, et al. Discovery and characterization of a selective, nonpeptidyl thrombopoietin receptor agonist. *Exp Hematol.* 2005;33(1):85-93. **13.** Bussel JB, G, Saleh MN, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. *N Engl J Med.* 2007;357(22):2237-2247. **14.** Jenkins J, Williams D, Deng Y, et al. Phase I study of eltrombopag, an oral, nonpeptide thrombopoietin receptor agonist. *Blood.* 2007;109:4739-4741. **15.** Data on File, GSK 2008.

Please see accompanying full Prescribing Information, including BOXED WARNING.

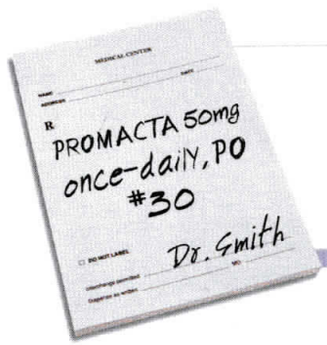
Generate Platelets[1]

Prescribers are required to understand the information in the Prescribing Information and be able to:

- Educate patients on the benefits and risks of treatment with PROMACTA, ensure that patients receive the Medication Guide, instruct them to read it, and encourage them to ask questions when considering PROMACTA. Patients may be educated by the enrolled prescriber or a healthcare provider under that prescriber's direction
- Review the PROMACTA *CARES* Prescriber Enrollment Forms, sign, and return the forms according to PROMACTA *CARES* Program instructions
- As part of the initial prescription process for PROMACTA, obtain the patient's signature on the Patient Enrollment and Consent form, sign it, place the original signed form in the patient's medical record, send a copy to PROMACTA *CARES*, and give a copy to the patient
- Report any serious adverse events associated with the use of PROMACTA to the PROMACTA *CARES* Call Center at 1-877-9-PROMACTA (1-877-977-6622) or to the FDA's MedWatch Program at 1-800-FDA-1088
- Report serious adverse events observed in patients receiving PROMACTA, including events actively solicited at 6-month intervals

Introducing PROMACTA— The first and only ORAL TPO agonist for the treatment of chronic ITP[1]

- PROMACTA is beneficial for chronic ITP therapy[1]
  - —Boosts platelet counts to ≥50,000/mcL
  - —Demonstrates a consistent response regardless of concomitant ITP therapy or splenectomy status
  - —Offers once-daily, oral dosing
- PROMACTA is available only through a restricted distribution program called PROMACTA *CARES*. Under PROMACTA *CARES*, only prescribers, pharmacies, and patients registered with the program are able to prescribe, dispense, and receive PROMACTA. This program provides educational materials and a mechanism for the proper use of PROMACTA. To enroll in PROMACTA *CARES*, call 1-877-9-PROMACTA (1-877-977-6622).[1]



The recommended starting dose of PROMACTA is 50 mg once daily, and may be increased to 75 mg or reduced to 25 mg once daily[1]

PROMACTA may cause hepatotoxicity. Increases in serum aminotransferase levels and bilirubin were observed in patients treated with PROMACTA. Liver chemistries must be measured before the initiation of treatment and regularly during treatment with PROMACTA.

Discontinuation of PROMACTA may result in worsened thrombocytopenia than was present prior to therapy with PROMACTA. Monitor weekly complete blood counts (CBCs), including platelet counts for at least 4 weeks after discontinuation of PROMACTA.

Please see accompanying full Prescribing Information, including BOXED WARNING.

For more information about PROMACTA, visit **www.PROMACTACARES.com**.

GlaxoSmithKline

NEW
PROMACTA®
(eltrombopag)
25mg, 50mg tablets