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.**

RECENT MAJOR CHANGES

Dosage and Administration, Initial Dose Regimen. (2.1)	XX/2011
Warnings and Precautions, Thrombotic/Thromboembolic Complications. (5.4)	XX/2011

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 initial dose of PROMACTA is 50 mg once daily for most patients. (2)
- Reduce the initial dose in patients with hepatic impairment (Child-Pugh Class A, B, C) and/or patients of East Asian ancestry. (2.1)
- Give on an empty stomach (1 hour before or 2 hours after a meal). (2)
- Allow a 4-hour interval between PROMACTA and other medications, foods, or supplements containing polyvalent cations (e.g., iron, calcium, aluminum, magnesium, selenium, and zinc). (2, 7.4)
- Adjust the daily dose to achieve and maintain a platelet count ≥50 x 10^9/L in order to reduce the risk for bleeding. (2)
- Do not exceed a daily dose of 75 mg. (2)
- Discontinue PROMACTA if the platelet count does not increase after 4 weeks at the maximum dose; also discontinue PROMACTA for important liver test abnormalities or excessive platelet count responses. (2)

DOSAGE FORMS AND STRENGTHS

25 mg, 50 mg, and 75 mg tablets. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to 25 mg, 50 mg, or 75 mg of eltrombopag free acid. (3)

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)
- 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 recurrence of thrombocytopenia. 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 (1-877-977-6622). (5.8)

ADVERSE REACTIONS

The most common adverse reactions (occurring in ≥3% of patients receiving PROMACTA and at a higher rate in PROMACTA versus placebo) were: nausea, diarrhea, upper respiratory tract infection, vomiting, increased ALT, myalgia, urinary tract infection, oropharyngeal pain, increased AST, pharyngitis, back pain, influenza, paresthesia, and rash. (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 and BCRP transporters. Monitor patients closely for signs and symptoms of excessive exposure to the drugs that are substrates of OATP1B1 and BCRP (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 as antacids, dairy products, and mineral supplements. (7.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: PROMACTA may cause fetal harm. Enroll pregnant patients in the PROMACTA pregnancy registry by calling 1-888-825-5249. (8.1)
- Nursing Mothers: A decision should be made to discontinue PROMACTA or nursing, taking into account the importance of PROMACTA to the mother. (8.3)
- Reduce the initial dose in patients with hepatic impairment (Child-Pugh Class A, B, C). (8.6)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE.

Revised: Month/YEAR

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK FOR HEPATOTOXICITY

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 the 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.**

Because of the risk for hepatotoxicity and other risks *[see Warnings and Precautions (5.1-5.6)]*, 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. To enroll in PROMACTA *CARES*, call 1-877-9-PROMACTA *[see Warnings and Precautions (5.8)]*.

1 INDICATIONS AND USAGE

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.

2 DOSAGE AND ADMINISTRATION

Only prescribers enrolled in PROMACTA *CARES* may prescribe PROMACTA *[see Warnings and Precautions (5.8)]*.

Monitor liver tests (ALT, AST, and bilirubin) and complete blood counts (CBCs), including platelet counts and peripheral blood smears, prior to initiation of PROMACTA and throughout therapy with PROMACTA. If bilirubin is elevated, perform fractionation. Monitor CBCs, including platelet counts, for at least 4 weeks following discontinuation of PROMACTA *[see Warnings and Precautions (5.3)]*. In clinical studies, platelet counts generally increased

within 1 to 2 weeks after starting PROMACTA and decreased within 1 to 2 weeks after discontinuing PROMACTA *[see Clinical Studies (14)]*.

Use the lowest dose of PROMACTA to achieve and maintain a platelet count ≥50 x 10^9/L as necessary to reduce the risk for bleeding. Dose adjustments are based upon the platelet count response. Do not use PROMACTA in an attempt to normalize platelet counts *[see Warnings and Precautions (5.4)]*.

Take PROMACTA on an empty stomach (1 hour before or 2 hours after a meal) *[see Clinical Pharmacology (12.3)]*. Allow at least a 4-hour interval between PROMACTA and other medications (e.g., antacids), calcium-rich foods (e.g., dairy products and calcium fortified juices), or supplements containing polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, and zinc *[see Drug Interactions (7.4) and Clinical Pharmacology (12.3)]*.

2.1 Initial Dose Regimen

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, initiate PROMACTA at a reduced dose of 25 mg once daily *[see Clinical Pharmacology (12.3)]*.

For patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, C), initiate PROMACTA at a reduced dose of 25 mg once daily *[see Use in Specific Populations (8.6)]*.

For patients of East Asian ancestry with hepatic impairment (Child-Pugh Class A, B, C), initiate PROMACTA at a reduced dose of 25 mg once every other day *[see Clinical Pharmacology (12.3)]*.

2.2 Monitoring and Dose Adjustment

After initiating PROMACTA, adjust the dose to achieve and maintain a platelet count ≥50 x 10^9/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 Table 1. During therapy with PROMACTA, assess CBCs, including platelet count and peripheral blood smears, weekly until a stable platelet count has been achieved. Obtain CBCs including platelet counts and peripheral blood smears, monthly thereafter.

Table 1. Dose Adjustments of PROMACTA

Platelet Count Result	Dose Adjustment or Response
<50 x 10^9/L following at least 2 weeks of PROMACTA	Increase daily dose by 25 mg to a maximum of 75 mg/day.[a]
≥200 x 10^9/L to ≤400 x 10^9/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.
>400 x 10^9/L	Stop PROMACTA; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is <150 x 10^9/L, reinitiate therapy at a daily dose reduced by 25 mg.
>400 x 10^9/L after 2 weeks of therapy at lowest dose of PROMACTA	Discontinue PROMACTA.

[a] For patients taking 25 mg once every other day; increase the dose to 25 mg daily before increasing the dose amount by 25 mg.

In patients with 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.

2.3 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 *[see Warnings and Precautions (5.1)]*.

3 DOSAGE FORMS AND STRENGTHS

25 mg tablets — round, biconvex, orange, film-coated tablets debossed with GS NX3 and 25 on one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to 25 mg of eltrombopag free acid.

50 mg tablets — round, biconvex, blue, film-coated tablets debossed with GS UFU and 50 on one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to 50 mg of eltrombopag free acid.

75 mg tablets — round, biconvex, pink, film-coated tablets debossed with GS FSS and 75 on one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to 75 mg of eltrombopag free acid.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk for Hepatotoxicity

PROMACTA administration may cause hepatotoxicity. In the controlled clinical studies, one patient experienced Grade 4 (NCI Common Terminology Criteria for Adverse Events [NCI CTCAE] toxicity scale) elevations in serum liver test values during therapy with PROMACTA, worsening of underlying cardiopulmonary disease, and death. One patient in the placebo group experienced a Grade 4 liver test abnormality. Overall, serum liver test abnormalities (predominantly Grade 2 or less in severity) were reported in 11% and 7% of the PROMACTA and placebo groups, respectively. In the 3 controlled studies, four patients (1%) treated with PROMACTA and three patients in the placebo group (2%) discontinued treatment due to hepatobiliary laboratory abnormalities. Seven of the patients treated with PROMACTA in the controlled studies with hepatobiliary laboratory abnormalities were re-exposed to PROMACTA in the extension study. Six of these patients again experienced liver test abnormalities (predominantly Grade 1) resulting in discontinuation of PROMACTA in one patient. In the extension study, one additional patient had PROMACTA discontinued due to liver test abnormalities (≤Grade 3).

Measure serum ALT, 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 the 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. If the potential benefit for reinitiating treatment with PROMACTA 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 tests abnormalities persist, worsen or recur, then permanently discontinue PROMACTA.

Pharmacokinetic evaluations in patients with hepatic impairment show that plasma eltrombopag $AUC_{(0-\tau)}$ increases with increasing degree of hepatic impairment (as measured by Child-Pugh). Exercise caution when administering PROMACTA to patients with hepatic impairment (Child-Pugh Class A, B, C). Use a lower starting dose of PROMACTA in patients with any degree of hepatic impairment and monitor closely *[see Dosage and Administration (2.1) and Use in Specific Populations (8.6)]*.

5.2 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 fiber deposition within the bone marrow.

In the extension study, 151 patients have had bone marrow biopsies evaluated for increased reticulin and collagen fiber deposition. Bone marrow biopsies taken after 1 year of therapy showed predominantly myelofibrosis (MF) Grade 1 or less in 140/151 (93%) of patients. There were 11/151 (7%) of patients with MF Grade 2. Four patients had collagen deposition reported. One patient with a preexisting MF Grade 1 developed a MF Grade 2 and subsequently discontinued treatment with PROMACTA. Clinical studies have not excluded a risk of bone marrow fibrosis with cytopenias.

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, examine peripheral blood smears and CBCs monthly for new or worsening morphological abnormalities (e.g., teardrop and nucleated red blood cells, immature white blood cells) or cytopenias. If the patient develops new or worsening morphological abnormalities or cytopenias, discontinue treatment with PROMACTA and consider a bone marrow biopsy, including staining for fibrosis.

5.3 Recurrence of Thrombocytopenia and Hemorrhage Risk After Cessation of PROMACTA

Discontinuation of PROMACTA may result in recurrence of thrombocytopenia. This recurrence of 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 3 controlled clinical studies, transient decreases in platelet counts to levels lower than baseline were observed following discontinuation of treatment in 8% of patients in both the PROMACTA and placebo groups. Serious hemorrhagic events requiring the use of supportive ITP medications occurred in 4 severely thrombocytopenic patients within one month following the discontinuation of PROMACTA; none were reported among patients in the placebo group.

Following discontinuation of PROMACTA, obtain weekly CBCs, including platelet counts for at least 4 weeks and consider alternative treatments for recurrence of thrombocytopenia, according to current treatment guidelines *[see Adverse Reactions (6.1)]*.

5.4 Thrombotic/Thromboembolic Complications

Thrombotic/thromboembolic complications may result from excessive increases in platelet counts. Excessive doses of PROMACTA may increase platelet counts to a level that produces thrombotic/thromboembolic complications.

In the 3 controlled clinical studies, thrombotic/thromboembolic complications occurred in four patients in the groups that received PROMACTA and none in the placebo groups. Thrombotic/thromboembolic complications were also reported in the extension study. The thrombotic/thromboembolic complications included both venous and arterial events and were observed at low and normal platelet counts.

Use caution when administering PROMACTA to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, chronic liver disease). 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 as necessary to decrease the risk for bleeding *[see Dosage and Administration (2.2)]*.

In a controlled study in non-ITP thrombocytopenic patients with chronic liver disease undergoing elective invasive procedures (N = 292), the risk of thrombotic events was increased in patients treated with 75 mg PROMACTA once daily. Seven thrombotic complications (six patients) were reported in the group that received PROMACTA and three thrombotic complications were reported in the placebo group (two patients). All of the thrombotic complications reported in the group that received PROMACTA were of the portal venous system. Five of the six patients in the group that received PROMACTA experienced a thrombotic complication within 30 days of completing treatment with PROMACTA and at a platelet count above 200 x 10^9/L. The risk of portal venous thrombosis was increased in thrombocytopenic patients with chronic liver disease treated with 75 mg PROMACTA once daily for 2 weeks in preparation for invasive procedures.

Exercise caution when administering PROMACTA to patients with hepatic impairment (Child-Pugh Class A, B, C). Use a lower starting dose of PROMACTA in patients with any degree of hepatic impairment and monitor closely *[see Dosage and Administration (2.1)]*. PROMACTA is not indicated for the treatment of thrombocytopenia in patients with chronic liver disease.

5.5 Hematologic Malignancies and Progression of Malignancies

PROMACTA stimulation of the TPO receptor on the surface of hematopoietic cells may increase the risk for hematologic malignancies. In the controlled clinical studies, patients were treated with PROMACTA for a maximum of 6 months. During this period no hematologic malignancies were reported in patients treated with PROMACTA. One hematologic malignancy (non-Hodgkin's lymphoma) was reported in the extension study. PROMACTA is not indicated for the treatment of thrombocytopenia due to diseases or treatments that cause thrombocytopenia (e.g., myelodysplasia or chemotherapy) other than chronic ITP.

5.6 Laboratory Monitoring

Complete Blood Counts (CBCs): Monitor CBCs, including platelet counts and peripheral blood smears, prior to initiation, throughout, and following discontinuation of therapy with PROMACTA. 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 *[see Dosage and Administration (2) and Warnings and Precautions (5.2, 5.3)]*.

Liver Tests: Monitor serum liver tests (ALT, 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. 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 important liver test abnormalities *[see Warnings and Precautions (5.1)]*.

5.7 Cataracts

In the 3 controlled clinical studies, cataracts developed or worsened in 15 (7%) patients who received 50 mg PROMACTA daily and 8 (7%) placebo-group patients. 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 *[see Nonclinical Toxicology (13.2)]*. Perform a baseline ocular examination prior to administration of PROMACTA and, during therapy with PROMACTA, regularly monitor patients for signs and symptoms of cataracts.

5.8 PROMACTA Distribution Program

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). Prescribers and patients are required to understand the risks of therapy with PROMACTA. 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 the patient receives 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 the form, and return the form 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 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.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

In clinical studies, hemorrhage was the most common serious adverse reaction and most hemorrhagic reactions followed discontinuation of PROMACTA. Other serious adverse reactions included liver test abnormalities and thrombotic/thromboembolic complications *[see Warnings and Precautions (5.1, 5.4)]*.

The data described below reflect PROMACTA exposure to 446 patients with chronic ITP aged 18 to 85, of whom 65% were female across the ITP clinical development program including 3 placebo-controlled studies. PROMACTA was administered to 277 patients for at least 6 months and 202 patients for at least 1 year.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Table 2 presents the most common adverse drug reactions (experienced by ≥3% of patients receiving PROMACTA) from the 3 placebo-controlled studies, with a higher incidence in PROMACTA versus placebo.

Table 2. Adverse Reactions (≥3%) from Three Placebo-Controlled Studies

Preferred Term	PROMACTA 50mg n = 241 (%)	Placebo n = 128 (%)
Nausea	9	3
Diarrhea	9	7
Upper respiratory tract infection	7	6
Vomiting	6	<1
Increased ALT	5	3
Myalgia	5	2
Urinary tract infection	5	3
Oropharyngeal pain	4	3
Increased AST	4	2
Pharyngitis	4	2
Back pain	3	2
Influenza	3	2
Paresthesia	3	2
Rash	3	2

In the 3 controlled clinical studies, alopecia, musculoskeletal pain, blood alkaline phosphatase increased, and dry mouth were the adverse reactions reported in 2% of patients treated with PROMACTA and in no patients who received placebo.

Among 299 patients with chronic ITP who received PROMACTA in the single-arm extension study, the adverse reactions occurred in a pattern similar to that seen in the placebo-controlled studies. Table 3 presents the most common treatment-related adverse reactions (experienced by ≥3% of patients receiving PROMACTA) from the extension study.

Table 3. Treatment-Related Adverse Reactions (≥3%) from Extension Study

Preferred Term	PROMACTA 50mg n = 299 (%)
Headache	10
Hyperbilirubinemia	6
ALT increased	6
Cataract	5
AST increased	4
Fatigue	4
Nausea	4

In a placebo-controlled trial of eltrombopag in non-ITP thrombocytopenic patients with chronic liver disease (CLD), six eltrombopag-treated patients and one patient in the placebo group developed portal vein thromboses *[see Warnings and Precautions (5.4)]*.

7 DRUG INTERACTIONS

7.1 Cytochrome P450

In vitro studies demonstrate that CYP1A2 and CYP2C8 are involved in the oxidative metabolism of eltrombopag. The significance of coadministration of PROMACTA with 1) moderate or strong inhibitors of CYP1A2 (e.g., ciprofloxacin, fluvoxamine) and CYP2C8 (e.g., gemfibrozil, trimethoprim); 2) inducers of CYP1A2 (e.g., tobacco, omeprazole) and CYP2C8 (e.g., rifampin); or 3) other substrates of these CYP enzymes on the systemic exposure of PROMACTA has not been established in clinical studies. Monitor patients for signs and symptoms of excessive eltrombopag exposure when PROMACTA is administered concomitantly with moderate or strong inhibitors of CYP1A2 or CYP2C8.

In vitro, eltrombopag is an inhibitor of CYP2C8 and CYP2C9 using paclitaxel and diclofenac as the probe substrates. A clinical study where PROMACTA 75 mg once daily was administered for 7 days to 24 healthy male subjects did not show inhibition or induction of the metabolism of a combination of probe substrates for CYP1A2 (caffeine), CYP2C19 (omeprazole), CYP2C9 (flurbiprofen), or CYP3A4 (midazolam) in humans. Probe substrates for CYP2C8 were not evaluated in this study.

7.2 Transporters

In vitro studies demonstrate that eltrombopag is an inhibitor of the organic anion transporting polypeptide OATP1B1 and breast cancer resistance protein (BCRP) and can

increase the systemic exposure of other drugs that are substrates of these transporters (e.g., benzylpenicillin, atorvastatin, fluvastatin, pravastatin, rosuvastatin, methotrexate, nateglinide, repaglinide, rifampin, doxorubicin). Administration of 75 mg of PROMACTA once daily for 5 days with a single 10 mg dose of the OATP1B1 and BCRP substrate, rosuvastatin, to 39 healthy adult subjects increased plasma rosuvastatin $AUC_{0-\infty}$ by 55% and C_{max} by 103%.

Use caution when concomitantly administering PROMACTA and drugs that are substrates of OATP1B1 or BCRP. Monitor patients closely for signs and symptoms of excessive exposure to the drugs that are substrates of OATP1B1 or BCRP and consider reduction of the dose of these drugs, if appropriate. In clinical trials with eltrombopag, a dose reduction of rosuvastatin by 50% was recommended for coadministration with eltrombopag.

In vitro studies demonstrate that eltrombopag is a BCRP substrate. The effect of co-administration of PROMACTA with moderate or strong BCRP inhibitors or inducers on the systemic exposure of PROMACTA has not been evaluated in clinical studies. Monitor patients closely for signs or symptoms of excessive exposure to PROMACTA when concomitantly administered with moderate or strong inhibitors of BCRP.

7.3 UDP-glucuronosyltransferases (UGTs)

In vitro studies demonstrate that eltrombopag is an inhibitor of UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15, enzymes involved in the metabolism of multiple drugs, such as acetaminophen, narcotics, and nonsteroidal anti-inflammatory drugs (NSAIDs). The significance of this inhibition on the potential for increased systemic exposure of drugs that are substrates of these UGTs following coadministration with PROMACTA has not been evaluated in clinical studies. Monitor patients closely for signs or symptoms of excessive exposure to these drugs when concomitantly administered with PROMACTA.

In vitro studies demonstrate that UGT1A1 and UGT1A3 are responsible for the glucuronidation of PROMACTA. The significance of coadministration of PROMACTA with moderate or strong inhibitors or inducers on the systemic exposure of PROMACTA has not been evaluated in clinical studies. Monitor patients closely for signs or symptoms of excessive exposure to PROMACTA when concomitantly administered with moderate or strong inhibitors of UGT1A1 or UGT1A3.

7.4 Polyvalent Cations (Chelation)

Eltrombopag chelates polyvalent cations (such as iron, calcium, aluminum, magnesium, selenium, and zinc) in foods, mineral supplements, and antacids. In a clinical study, administration of PROMACTA with a polyvalent cation-containing antacid (1,524 mg aluminum hydroxide, 1,425 mg magnesium carbonate, and sodium alginate) decreased plasma eltrombopag systemic exposure by approximately 70%. The contribution of sodium alginate to this interaction is not known. PROMACTA must not be taken within 4 hours of any medications or products containing polyvalent cations such as antacids, dairy products, and mineral supplements to avoid significant reduction in PROMACTA absorption due to chelation *[see Dosage and Administration (2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of eltrombopag use in pregnancy. In animal reproduction and developmental toxicity studies, there was evidence of embryolethality and reduced fetal weights at maternally toxic doses. PROMACTA should be used in pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Pregnancy Registry: A pregnancy registry has been established to collect information about the effects of PROMACTA during pregnancy. Physicians are encouraged to register pregnant patients, or pregnant women may enroll themselves in the PROMACTA pregnancy registry by calling 1-888-825-5249.

In an early embryonic development study, female rats received oral eltrombopag at doses of 10, 20, or 60 mg/kg/day (0.8, 2, and 6 times the human clinical exposure based on AUC). Increased pre- and post-implantation loss and reduced fetal weight were observed at the highest dose which also caused maternal toxicity.

Eltrombopag was administered orally to pregnant rats at 10, 20, or 60 mg/kg/day (0.8, 2, and 6 times the human clinical exposure based on AUC). Decreased fetal weights (6% to 7%) and a slight increase in the presence of cervical ribs were observed at the highest dose which also caused maternal toxicity. However, no evidence of major structural malformations was observed.

Pregnant rabbits were treated with oral eltrombopag doses of 30, 80, or 150 mg/kg/day (0.04, 0.3, and 0.5 times the human clinical exposure based on AUC). No evidence of fetotoxicity, embryolethality, or teratogenicity was observed.

In a pre- and post-natal developmental toxicity study in pregnant rats (F0), no adverse effects on maternal reproductive function or on the development of the offspring (F1) were observed at doses up to 20 mg/kg/day (2 times the human clinical exposure based on AUC). Eltrombopag was detected in the plasma of offspring (F1). The plasma concentrations in pups increased with dose following administration of drug to the F0 dams.

8.3 Nursing Mothers

It is not known whether eltrombopag is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from PROMACTA, a decision should be made whether to discontinue nursing or to discontinue PROMACTA taking into account the importance of PROMACTA to the mother.

8.4 Pediatric Use

The safety and efficacy of PROMACTA in pediatric patients have not been established.

8.5 Geriatric Use

Of the 106 patients in 2 randomized clinical studies of PROMACTA 50 mg dose, 22% were 65 years of age and older, and 9% were 75 years of age and older. No overall differences in safety or efficacy have been observed between older and younger patients in the placebo-controlled studies, but greater sensitivity of some older individuals cannot be ruled out. In general, dose adjustment for an elderly patient should be cautious, reflecting the greater

frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

The disposition of PROMACTA following a single 50 mg dose in patients with mild, moderate, and severe hepatic impairment was compared to subjects with normal hepatic function. The degree of hepatic impairment was based on Child-Pugh score. Plasma eltrombopag $AUC_{0-\infty}$ was 41% higher in patients with mild hepatic impairment (Child-Pugh A) compared to subjects with normal hepatic function. Plasma eltrombopag $AUC_{0-\infty}$ was approximately 2-fold higher in patients with moderate (Child-Pugh B) and severe hepatic impairment (Child-Pugh C). The half-life of PROMACTA was prolonged 2-fold in these patients. This clinical study did not evaluate protein binding effects.

Similar results were seen in a population pharmacokinetic (PK) analysis in thrombocytopenic patients with chronic liver disease following repeat doses of eltrombopag. However, compared to healthy volunteers, the population PK analysis demonstrated that mild hepatic impairment resulted in an 87% to 110% higher plasma eltrombopag $AUC_{(0-\tau)}$ and patients with moderate hepatic impairment had approximately 141% to 240% higher plasma eltrombopag $AUC_{(0-\tau)}$ values. The half-life of PROMACTA was prolonged 3-fold in patients with mild hepatic impairment and 4-fold in patients with moderate hepatic impairment. This clinical study did not evaluate protein binding effects.

A reduction in the initial dose of PROMACTA is recommended for patients with hepatic impairment (Child-Pugh Class A, B, C) *[see Dosage and Administration (2.1) and Warnings and Precautions (5.1)]*.

8.7 Renal Impairment

The disposition of a single 50 mg dose of PROMACTA in patients with mild, moderate and severe renal impairment was compared to subjects with normal renal function. Average total plasma eltrombopag $AUC_{0-\infty}$ was 32% to 36% lower in subjects with mild to moderate renal impairment and 60% lower in subjects with severe renal impairment compared with healthy subjects. The effect of renal impairment on unbound (active) eltrombopag exposure, has not been assessed.

No adjustment in the initial PROMACTA dose is needed for patients with renal impairment. Closely monitor patients with impaired renal function when administering PROMACTA.

10 OVERDOSAGE

In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications.

In one report, a subject who ingested 5,000 mg of PROMACTA had a platelet count increase to a maximum of 929 x 10^9/L at 13 days following the ingestion. The patient also experienced rash, bradycardia, ALT/AST elevations, and fatigue. The patient was treated with gastric lavage, oral lactulose, intravenous fluids, omeprazole, atropine, furosemide, calcium,

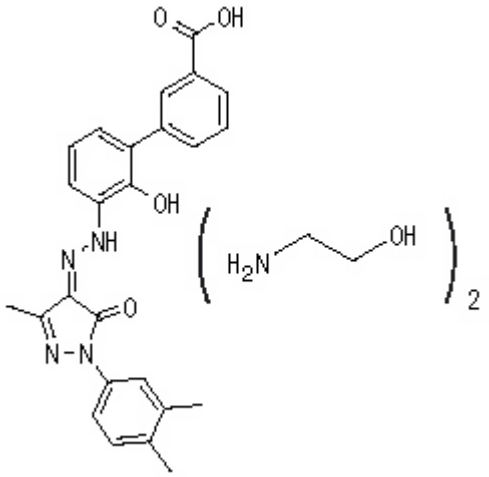
dexamethasone, and plasmapheresis; however, the abnormal platelet count and liver test abnormalities persisted for 3 weeks. After 2 months follow-up, all events had resolved without sequelae.

In case of an overdose, consider oral administration of a metal cation-containing preparation, such as calcium, aluminum, or magnesium preparations to chelate eltrombopag and thus limit absorption. Closely monitor platelet counts. Reinitiate treatment with PROMACTA in accordance with dosing and administration recommendations *[see Dosage and Administration (2.2)]*.

11 DESCRIPTION

PROMACTA (eltrombopag) Tablets contain eltrombopag olamine, a small molecule thrombopoietin (TPO) receptor agonist for oral administration. Eltrombopag interacts with the transmembrane domain of the TPO receptor (also known as cMpl) leading to increased platelet production. Each tablet contains eltrombopag olamine in the amount equivalent to 25 mg, 50 mg, or 75 mg of eltrombopag free acid.

Eltrombopag olamine is a biphenyl hydrazone. The chemical name for eltrombopag olamine is 3'-{(2Z)-2-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene]hydrazino}-2'-hydroxy-3-biphenylcarboxylic acid - 2-aminoethanol (1:2). It has the molecular formula $C_{25}H_{22}N_4O_4 \bullet 2(C_2H_7NO)$. The molecular weight is 564.65 for eltrombopag olamine and 442.5 for eltrombopag free acid. Eltrombopag olamine has the following structural formula:



Eltrombopag olamine is practically insoluble in aqueous buffer across a pH range of 1 to 7.4, and is sparingly soluble in water.

The inactive ingredients of PROMACTA are: **Tablet Core:** magnesium stearate, mannitol, microcrystalline cellulose, povidone, and sodium starch glycolate. **Coating:** hypromellose, polyethylene glycol 400, titanium dioxide, and FD&C Yellow No. 6 aluminum lake (25 mg tablet), FD&C Blue No. 2 aluminum lake (50 mg tablet), or Iron Oxide Red and Iron Oxide Black (75 mg tablet).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Eltrombopag is an orally bioavailable, small-molecule TPO-receptor agonist that interacts with the transmembrane domain of the human TPO-receptor and initiates signaling cascades that induce proliferation and differentiation of megakaryocytes from bone marrow progenitor cells.

12.3 Pharmacokinetics

A population pharmacokinetic model analysis suggests that the pharmacokinetic profile for eltrombopag following oral administration is best described by a 2-compartment model. Based on this model, the estimated exposures of eltrombopag after administration to patients with ITP are shown in Table 3.

Table 3. Geometric Mean (95% Confidence Intervals) of Steady-State Plasma Eltrombopag Pharmacokinetic Parameters in Adults With Idiopathic Thrombocytopenic Purpura

Regimen of PROMACTA	$AUC_{(0-\tau)}$ (mcg.hr/mL)	C_{max} (mcg/mL)
50 mg once daily (N = 34)	108 (88, 134)	8.01 (6.73, 9.53)
75 mg once daily (N = 26)	168 (143, 198)	12.7 (11.0, 14.5)

Absorption: Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. Based on urinary excretion and biotransformation products eliminated in feces, the oral absorption of drug-related material following administration of a single 75 mg solution dose was estimated to be at least 52%.

An open-label, randomized, crossover study was conducted to assess the effect of food on the bioavailability of eltrombopag. A standard high-fat breakfast significantly decreased plasma eltrombopag $AUC_{0-\infty}$ by approximately 59% and C_{max} by 65% and delayed t_{max} by 1 hour. The calcium content of this meal may have also contributed to this decrease in exposure.

Distribution: The concentration of eltrombopag in blood cells is approximately 50% to 79% of plasma concentrations based on a radiolabel study. *In vitro* studies suggest that eltrombopag is highly bound to human plasma proteins (>99%). Eltrombopag is a substrate of BCRP, but is not a substrate for P-glycoprotein (P-gp) or OATP1B1.

Metabolism: Absorbed eltrombopag is extensively metabolized, predominantly through pathways including cleavage, oxidation, and conjugation with glucuronic acid, glutathione, or cysteine. *In vitro* studies suggest that CYP1A2 and CYP2C8 are responsible for the oxidative metabolism of eltrombopag. UGT1A1 and UGT1A3 are responsible for the glucuronidation of eltrombopag.

Elimination: The predominant route of eltrombopag excretion is via feces (59%), and 31% of the dose is found in the urine. Unchanged eltrombopag in feces accounts for approximately 20% of the dose; unchanged eltrombopag is not detectable in urine. The plasma

elimination half-life of eltrombopag is approximately 21 to 32 hours in healthy subjects and 26 to 35 hours in ITP patients.

Race: The influence of East Asian ethnicity (i.e., Japanese, Chinese, Taiwanese, and Korean) on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic approach in 111 healthy adults (31 East Asians) and 88 patients with ITP (18 East Asians). After adjusting for body weight differences, East Asians had approximately 50% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to non-East Asian patients who were predominantly Caucasian. In a separate population PK analysis of PROMACTA in 28 healthy adults (non-East Asians) and 79 patients with chronic liver disease (45 East Asians), East Asian patients had approximately 110% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to non-East Asian patients, after adjusting for body weight differences. A reduction in the initial dose of PROMACTA is recommended for patients of East Asian ancestry and East Asian patients with hepatic impairment (Child-Pugh Class A, B, C) *[see Dosage and Administration (2.1)]*.

An approximately 40% higher systemic eltrombopag exposure in healthy African-American subjects was noted in at least one clinical pharmacology study. The effect of African-American ethnicity on exposure and related safety and efficacy of eltrombopag has not been established.

Gender: The influence of gender on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic approach in 111 healthy adults (14 females) and 88 patients with ITP (57 females). After adjustment for body weight differences females had approximately 23% higher plasma eltrombopag $AUC_{(0-\tau)}$ values than males.

12.6 QT/QTc Prolongation

There is no indication of a QT/QTc prolonging effect of PROMACTA at doses up to 150 mg daily for 5 days. The effects of PROMACTA at doses up to 150 mg daily for 5 days (supratherapeutic doses) on the QT/QTc interval was evaluated in a double-blind, randomized, placebo- and positive-controlled (moxifloxacin 400 mg, single oral dose) crossover trial in healthy adult subjects. Assay sensitivity was confirmed by significant QTc prolongation by moxifloxacin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Eltrombopag does not stimulate platelet production in rats, mice, or dogs because of unique TPO receptor specificity. Data from these animals do not fully model effects in humans.

Eltrombopag was not carcinogenic in mice at doses up to 75 mg/kg/day or in rats at doses up to 40 mg/kg/day (exposures up to 4 times the human clinical exposure based on AUC).

Eltrombopag was not mutagenic or clastogenic in a bacterial mutation assay or in 2 *in vivo* assays in rats (micronucleus and unscheduled DNA synthesis, 10 times the human clinical exposure based on C_{max}). In the *in vitro* mouse lymphoma assay, eltrombopag was marginally positive (<3-fold increase in mutation frequency).

Eltrombopag did not affect female fertility in rats at doses up to 20 mg/kg/day (2 times the human clinical exposure based on AUC). Eltrombopag did not affect male fertility in rats at doses up to 40 mg/kg/day, the highest dose tested (3 times the human clinical exposure based on AUC).

13.2 Animal Pharmacology/Toxicology

Eltrombopag is phototoxic *in vitro*. There was no evidence of *in vivo* cutaneous or ocular phototoxicity in rodents.

Treatment-related cataracts were detected in rodents in a dose- and time-dependent manner. At ≥6 times the human clinical exposure based on AUC, cataracts were observed in mice after 6 weeks and in rats after 28 weeks of dosing. At ≥4 times the human clinical exposure based on AUC, cataracts were observed in mice after 13 weeks and in rats after 39 weeks of dosing. The clinical relevance of these findings is unknown *[see Warnings and Precautions (5.7)]*.

Renal tubular toxicity was observed in studies up to 14 days in duration in mice and rats at exposures that were generally associated with morbidity and mortality. Tubular toxicity was also observed in a 2-year oral carcinogenicity study in mice at doses of 25, 75, and 150 mg/kg/day. The exposure at the lowest dose was 1.2 times the human clinical exposure based on AUC. No similar effects were observed in mice after 13 weeks at exposures greater than those associated with renal changes in the 2-year study, suggesting that this effect is both dose- and time-dependent.

14 CLINICAL STUDIES

The efficacy and safety of PROMACTA in adult patients with chronic ITP were evaluated in 3 randomized double-blind, placebo-controlled studies and in an open-label extension study.

14.1 Studies 1 and 2

In studies 1 and 2, patients who had completed at least one prior ITP therapy and who had a platelet count $<30 \times 10^9$/L were randomized to receive either PROMACTA or placebo daily for up to 6 weeks, followed by 6 weeks off therapy. During the studies, PROMACTA or placebo was discontinued if the platelet count exceeded 200×10^9/L. The primary efficacy endpoint was response rate, defined as a shift from a baseline platelet count of $<30 \times 10^9$/L to $\geq 50 \times 10^9$/L at any time during the treatment period.

The median age of the patients was 50 years and 60% were female. Approximately 70% of the patients had received at least 2 prior ITP therapies (predominantly corticosteroids, immunoglobulins, rituximab, cytotoxic therapies, danazol, and azathioprine) and 40% of the patients had undergone splenectomy. The median baseline platelet counts (approximately 18×10^9/L) were similar among all treatment groups.

Study 1 randomized 114 patients (2:1) to PROMACTA 50 mg or placebo. Study 2 randomized 117 patients (1:1:1:1) among placebo or 1 of 3 dose regimens of PROMACTA, 30 mg, 50 mg, or 75 mg each administered daily.

Table 4 shows for each study the primary efficacy outcomes for the placebo groups and the patient groups who received the 50 mg daily regimen of PROMACTA.

Table 4. Studies 1 and 2 Platelet Count Response (≥50 x 10^9/L) Rates

Study	PROMACTA 50 mg Daily	Placebo
1	43/73 (59%)[a]	6/37 (16%)
2	19/27 (70%)[a]	3/27 (11%)

[a] *P* value <0.001 for PROMACTA versus placebo.

The platelet count response to PROMACTA was similar among patients who had or had not undergone splenectomy. 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. In the placebo and 50 mg dose groups of PROMACTA, the study drug was discontinued due to an increase in platelet counts to >200 x 10^9/L in 3% and 27% of the patients, respectively. The median duration of treatment with the 50 mg dose of PROMACTA was 42 days in Study 1 and 43 days in Study 2.

Of 7 patients who underwent hemostatic challenges, additional ITP medications were required in 3 of 3 placebo group patients and 0 of 4 patients treated with PROMACTA. Surgical procedures accounted for most of the hemostatic challenges. Hemorrhage requiring transfusion occurred in one placebo group patient and no patients treated with PROMACTA.

14.2 Study 3

In this study, 197 patients were randomized (2:1) to receive either PROMACTA 50 mg once daily (n = 135) or placebo (n = 62) for 6 months, during which time the dose of PROMACTA could be adjusted based on individual platelet counts. Patients were allowed to taper or discontinue concomitant ITP medications after being treated with PROMACTA for 6 weeks. Patients were permitted to receive rescue treatments at any time during the study as clinically indicated. The primary endpoint was the odds of achieving a platelet count ≥50 x 10^9/L and ≤400 x 10^9/L for patients receiving PROMACTA relative to placebo and was based on patient response profiles throughout the 6-month treatment period.

The median age of the patients treated with PROMACTA and placebo was 47 years and 52.5 years, respectively. Approximately half of the patients treated with PROMACTA and placebo (47% and 50%, respectively) were receiving concomitant ITP medication (predominantly corticosteroids) at randomization and had baseline platelet counts ≤15 x 10^9/L (50% and 48%, respectively). A similar percentage of patients treated with PROMACTA and placebo (37% and 34%, respectively) had a prior splenectomy.

In 134 patients who completed 26 weeks of treatment, a sustained platelet response (platelet count ≥50 x 10^9/L and ≤400 x 10^9/L for 6 out of the last 8 weeks of the 26-week treatment period in the absence of rescue medication at any time) was achieved by 60% of patients treated with PROMACTA, compared to 10% of patients treated with placebo

(splenectomized patients: PROMACTA 51%, placebo 8%; non-splenectomized patients: PROMACTA 66%, placebo 11%). The proportion of responders in the PROMACTA treatment group was between 37% and 56% compared to 7% and 19% in the placebo treatment group for all on-therapy visits. Patients treated with PROMACTA were significantly more likely to achieve a platelet count between 50 x 10^9/L and 400 x 10^9/L during the entire 6-month treatment period compared to those patients treated with placebo.

Outcomes of treatment are presented in Table 5 for all patients enrolled in the study.

Table 5. Outcomes of Treatment from the Study 3

Outcome	PROMACTA N = 135	Placebo N = 62
Mean number of weeks with platelet counts ≥50 x 10^9/L	11.3	2.4
Requiring rescue therapy, n (%)[a]	24 (18)	25 (40)

Among 94 patients receiving other ITP therapy at baseline, 37 (59%) of 63 patients in the PROMACTA group and 10 (32%) of 31 patients in the placebo group discontinued concomitant therapy at some time during the study.

14.3 Extension Study

Patients who completed any prior clinical study with PROMACTA were enrolled in an open-label, single-arm study in which attempts were made to decrease the dose or eliminate the need for any concomitant ITP medications. PROMACTA was administered to 299 patients; 249 completed 6 months, 210 patients completed 12 months, and 138 patients completed 24 months of therapy. The median baseline platelet count was 18 x 10^9/L prior to administration of PROMACTA.

16 HOW SUPPLIED/STORAGE AND HANDLING

The 25 mg tablets are round, biconvex, orange, film-coated tablets debossed with GS NX3 and 25 on one side and are available in bottles of 30: NDC 0007-4640-13.

The 50 mg tablets are round, biconvex, blue, film-coated tablets debossed with GS UFU and 50 on one side and are available in bottles of 30: NDC 0007-4641-13.

The 75 mg tablets are round, biconvex, pink, film-coated tablets debossed with GS FFS and 75 on one side and are available in bottles of 30: NDC 0007-4642-13.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

17.1 Information for Patients

Prior to treatment, patients should fully understand the risks and benefits of PROMACTA. Inform patients that the risks associated with long-term administration of PROMACTA are unknown and that they must enroll in PROMACTA *CARES*, which provides for the proper use of PROMACTA in ITP patients.

Inform patients of the following risks and considerations for PROMACTA:

- Therapy with PROMACTA is administered to achieve and maintain a platelet count ≥50 x 10^9/L as necessary to reduce the risk for bleeding; PROMACTA is not used to normalize platelet counts.
- Therapy with PROMACTA may be associated with hepatobiliary laboratory abnormalities. Monitor serum liver tests (ALT, 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.
- Inform patients that they should report any of the following signs and symptoms of liver problems to their healthcare provider right away.
  - yellowing of the skin or the whites of the eyes (jaundice),
  - unusual darkening of the urine,
  - unusual tiredness,
  - right upper stomach area pain.
- Following discontinuation of PROMACTA, thrombocytopenia and risk of bleeding may reoccur, particularly if PROMACTA is discontinued while the patient is on anticoagulants or antiplatelet agents.
- Therapy with PROMACTA increases the risk of reticulin fiber formation within the bone marrow, and further fiber formation may progress to marrow fibrosis. Detection of peripheral blood cell abnormalities may necessitate a bone marrow examination.
- Too much PROMACTA may result in excessive platelet counts and a risk for thrombotic/thromboembolic complications.
- PROMACTA stimulates certain bone marrow cells to make platelets and may increase the risk for progression of underlying MDS or hematological malignancies.
- Platelet counts and CBCs, including peripheral blood smears, must be performed weekly until a stable dose of PROMACTA has been achieved; thereafter, platelet counts and CBCs, including peripheral blood smears, must be performed monthly while taking PROMACTA.
- Patients must be closely monitored with weekly platelet counts and CBCs for at least 4 weeks following discontinuation of PROMACTA.
- Even during therapy with PROMACTA, patients should continue to avoid situations or medications that may increase the risk for bleeding.
- Patients must be advised to keep at least a 4-hour interval between PROMACTA and foods, mineral supplements, and antacids which contain polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, and zinc.

PROMACTA is a registered trademark of GlaxoSmithKline.

GlaxoSmithKline
Research Triangle Park, NC 27709

Month YEAR
PRM:XPI

MEDICATION GUIDE

PROMACTA® (pro-MAC-ta)
(eltrombopag)
Tablets

Read this Medication Guide before you start taking PROMACTA and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about PROMACTA?

PROMACTA can cause serious side effects, including:

- **Liver problems.** PROMACTA may damage your liver and cause serious illness and death. You must have blood tests to check your liver before you start taking PROMACTA and during treatment with PROMACTA. Your healthcare provider will order these blood tests. In some cases PROMACTA treatment may need to be stopped. Tell your healthcare provider right away if you have any of these signs and symptoms of liver problems:
  - yellowing of the skin or the whites of the eyes (jaundice)
  - unusual darkening of the urine
  - unusual tiredness
  - right upper stomach area pain
- **Bone marrow changes (increased reticulin and possible bone marrow fibrosis).** Long-term use of PROMACTA may cause changes in your bone marrow. These changes may lead to abnormal blood cells or your body making less blood cells. The mild form of these bone marrow changes is called “increased reticulin” which may progress to a more severe form called “fibrosis”. The mild form may cause no problems while the severe form may cause life-threatening blood problems. Signs of bone marrow changes may show up as abnormal results in your blood tests. Your healthcare provider will decide if abnormal blood test results mean that you should have bone marrow tests or if you should stop taking PROMACTA.
- **Recurrence of low blood platelet count (thrombocytopenia) and risk of bleeding shortly after stopping PROMACTA.** When you stop taking PROMACTA, your blood platelet count may return to a similar low platelet count as before you started taking PROMACTA. These effects are

most likely to happen within 4 weeks after you stop taking PROMACTA. The recurrence of low platelet counts may increase your risk of bleeding, especially if you take a blood thinner or other medicines that affect platelets. Your healthcare provider will check your blood platelet counts for at least 4 weeks after you stop taking PROMACTA. Call your healthcare provider right away to report any bruising or bleeding.

- **High platelet counts and higher chance for blood clots.** Your chance of getting a blood clot is increased if your platelet count is too high during treatment with PROMACTA. Your chance of getting a blood clot may also be increased during treatment with PROMACTA if you have normal or low platelet counts. You may have severe complications or die from some forms of blood clots, such as clots that travel to the lungs or that cause heart attacks or strokes. Your healthcare provider will check your blood platelet counts, and change your dose or stop PROMACTA if your platelet counts get too high. Tell your healthcare provider right away if you have signs and symptoms of a blood clot in the leg, such as swelling, pain, or tenderness in your leg.
  Patients with chronic liver disease may be at risk for a type of blood clot in the stomach area. Stomach area pain may be a symptom of this type of blood clot.
- **Worsening of blood cancers.** PROMACTA is not for use in patients with blood cancer or a precancerous condition called myelodysplastic syndrome (MDS). If you have one of these conditions, PROMACTA may worsen your cancer or condition and may cause you to die sooner.
- **New or worsened cataracts (a clouding of the lens in the eye).** New or worsened cataracts have happened in people taking PROMACTA. Your healthcare provider will check your eyes before and during your treatment with PROMACTA. Tell your healthcare provider about any changes in your eyesight while taking PROMACTA.

When you are being treated with PROMACTA, your healthcare provider will closely monitor your dose of PROMACTA and blood tests, including platelet counts and liver tests.

PROMACTA is available only through a program called “PROMACTA *CARES*”. To receive PROMACTA, you must talk to your healthcare provider, understand the benefits and risks of PROMACTA and agree to enroll into PROMACTA *CARES*.

- During therapy with PROMACTA, your healthcare provider may change your dose of PROMACTA, depending upon the change in your blood

platelet count. You must have blood platelet count tests done before, during and after your therapy with PROMACTA.

See "What are the possible side effects of PROMACTA?" for other side effects of PROMACTA.

What is PROMACTA?

PROMACTA is a prescription medicine used to treat low blood platelet counts in adults with chronic immune (idiopathic) thrombocytopenic purpura (ITP), when other medicines to treat your ITP or surgery to remove the spleen have not worked well enough.

PROMACTA is used to try to keep your platelet count about 50,000 per microliter in order to lower your risk for bleeding. PROMACTA is not used to make your platelet count normal.

PROMACTA is only:

- prescribed by healthcare providers who are enrolled in PROMACTA *CARES*.
- given to people who are enrolled in PROMACTA *CARES*.

It is not known if PROMACTA works or if it is safe in people under the age of 18 years.

PROMACTA is for treatment of certain people with low platelet counts caused by chronic ITP, not low platelet counts caused by other conditions or diseases.

What should I tell my healthcare provider before taking PROMACTA?

Before you take PROMACTA, tell your healthcare provider if you:

- have liver or kidney problems
- have or had a blood clot
- have a history of cataracts
- have had surgery to remove your spleen (splenectomy)
- have a bone marrow problem, including a blood cancer or Myelodysplastic Syndrome (MDS)
- have bleeding problems
- are Asian and you are of Chinese, Japanese, Taiwanese, or Korean ancestry, you may need a lower dose of PROMACTA.
- have any other medical conditions

- are pregnant, think you may be pregnant, or plan to get pregnant. It is not known if PROMACTA will harm an unborn baby.
  Pregnancy Registry: There is a registry for women who become pregnant during treatment with PROMACTA. If you become pregnant, consider this registry. The purpose of the registry is to collect safety information about the health of you and your baby. Contact the registry as soon as you become aware of the pregnancy, or ask your healthcare provider to contact the registry for you. You and your healthcare provider can get information and enroll in the registry by calling 1-888-825-5249.
- are breast-feeding or plan to breast-feed. It is not known if PROMACTA passes into your breast milk. You and your healthcare provider should decide whether you will take PROMACTA or breast-feed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal products. PROMACTA may affect the way certain medicines work. Certain other medicines may affect the way PROMACTA works.

Especially tell your healthcare provider if you take:
- certain medicines used to treat high cholesterol, called “statins”.
- a blood thinner medicine.

Certain medicines may keep PROMACTA from working correctly. Take PROMACTA either 4 hours before or 4 hours after taking these products:
- antacids used to treat stomach ulcers or heartburn.
- multivitamins or products that contain iron, calcium, aluminum, magnesium, selenium, and zinc which may be found in mineral supplements.

Ask your healthcare provider if you are not sure if your medicine is one that is listed above.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take PROMACTA?

To receive PROMACTA, you must first talk with your healthcare provider and understand the benefits and risks of PROMACTA. You must agree to and follow all of the instructions in PROMACTA *CARES*.

- Before you can begin to receive PROMACTA, your healthcare provider will:
  - explain PROMACTA *CARES* to you.
  - answer all of your questions about PROMACTA and PROMACTA *CARES*.
  - make sure you read this PROMACTA Medication Guide.
  - have you sign the PROMACTA *CARES* Patient Enrollment Form.
- Take PROMACTA exactly as your healthcare provider tells you. Do not stop using PROMACTA without talking with your healthcare provider first. Do not change your dose or schedule for taking PROMACTA unless your healthcare provider tells you to change it.
- Take PROMACTA on an empty stomach, either 1 hour before or 2 hours after eating food.
- Take PROMACTA at least 4 hours before or 4 hours after eating dairy products and calcium fortified juices.
- If you miss a dose of PROMACTA, wait and take your next scheduled dose. Do not take more than one dose of PROMACTA in one day.
- If you take too much PROMACTA, you may have a higher chance of serious side effects. Call your healthcare provider right away.
- Your healthcare provider will check your platelet count every week and change your dose of PROMACTA as needed. This will happen every week until your healthcare provider decides that your dose of PROMACTA can stay the same. After that, you will need to have blood tests every month. When you stop taking PROMACTA, you will need to have blood tests for at least 4 weeks to check if your platelet count drops too low.
- Tell your healthcare provider about any bruising or bleeding that happens while you take and after you stop taking PROMACTA.

What should I avoid while taking PROMACTA?

Avoid situations and medicines that may increase your risk of bleeding.

What are the possible side effects of PROMACTA?

PROMACTA may cause serious side effects.

See **“What is the most important information I should know about PROMACTA?”.**

The most common side effects of PROMACTA are:

- nausea
- diarrhea
- upper respiratory tract infection; symptoms may include runny nose, stuffy nose, and sneezing

- vomiting
- muscle aches
- urinary tract infections; symptoms may include frequent or urgent need to urinate, low fever in some patients, pain or burning with urination
- pain or swelling (inflammation) in your throat or mouth (oropharyngeal pain and pharyngitis)
- abnormal liver function tests
- abnormal skin sensations such as tingling, itching, or burning
- back pain
- 'flu' symptoms (influenza); symptoms may include fever, headache, tiredness, cough, sore throat, and body aches
- rash

These are not all the possible side effects of PROMACTA. Tell your healthcare provider if you have any side effect that bothers you or that does not go away. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PROMACTA Tablets?

- Store at room temperature between 59°F and 86°F (15°C and 30°C).
- **Keep PROMACTA and all medicines out of the reach of children.**

General information about the safe and effective use of PROMACTA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use PROMACTA for a condition for which it was not prescribed. Do not give PROMACTA to other people even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about PROMACTA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about PROMACTA that is written for healthcare professionals.

For more information, go to www.PROMACTA.com or call toll-free 1-888-825-5249.

What are the ingredients in PROMACTA?

Active Ingredient: eltrombopag olamine.

Inactive Ingredients:

- Tablet Core: Magnesium stearate, mannitol, microcrystalline cellulose, povidone, and sodium starch glycolate.
- Coating: Hypromellose, polyethylene glycol 400, titanium dioxide, and FD&C Yellow No. 6 aluminum lake (25 mg tablet), FD&C Blue No. 2 aluminum lake (50 mg tablet), or Iron Oxide Red and Iron Oxide Black (75 mg tablet).

PROMACTA is a registered trademark of GlaxoSmithKline.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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