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. PROMACTA, in combination with interferon and ribavirin in patients with chronic hepatitis C, may increase the risk of hepatic decompensation. (5.1, 5.2)

- **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) in patients with normal liver function or ≥3X baseline in patients with pre-treatment elevations in transaminases 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----------

Boxed Warning	11/2012
Indications and Usage (1)	11/2012
Dosage and Administration (2.2)	11/2012
Warnings and Precautions (5.1, 5.2, 5.4, 5.6)	11/2012

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

PROMACTA is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. (1.1)

PROMACTA is indicated for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. (1.2)

Limitations of use:

- PROMACTA should not be used in an attempt to normalize platelet counts. (1.3)
- PROMACTA should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding. (1.3)
- PROMACTA should be used only in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon therapy or limits the ability to maintain optimal interferon-based therapy. (1.3)
- Safety and efficacy have not been established in combination with direct acting antiviral agents approved for treatment of chronic hepatitis C genotype 1 infection. (1.3)

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

- Take 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)
- **Chronic ITP:** Initiate PROMACTA at 50 mg once daily for most patients. Reduce the initial dose in patients with hepatic impairment and/or patients of East Asian ancestry. Adjust to maintain a platelet count ≥50 x 10^9/L. Do not exceed 75 mg per day. (2.1)
- **Chronic Hepatitis C-associated thrombocytopenia:** Initiate PROMACTA at 25 mg once daily for all patients. Adjust to achieve a target platelet count required to initiate antiviral therapy. Do not exceed a daily dose of 100 mg. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

12.5 mg, 25 mg, 50 mg, 75 mg, and 100 mg tablets. (3)

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

None. (4)

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

- Hepatotoxicity: Monitor liver function before and during therapy. (5.1)
- Hepatic decompensation in patients with chronic hepatitis C: Monitor patients with low albumin levels or with MELD score ≥10 at baseline. (5.2)
- Thrombotic/thromboembolic complications: Portal vein thrombosis has been reported in patients with chronic liver disease receiving PROMACTA. Monitor platelet counts regularly. (5.4)

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

- The most common adverse reactions in ITP patients (≥3% and greater than 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)
- The most common adverse reactions in thrombocytopenic patients with chronic hepatitis C (≥10% and greater than placebo) were: anemia, pyrexia, fatigue, headache, nausea, diarrhea, decreased appetite, influenza-like illness, asthenia, insomnia, cough, pruritus, chills, myalgia, alopecia, and peripheral edema. (6.2)

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 ----------

- PROMACTA must not be taken within 4 hours of any medications or products containing polyvalent cations such as antacids, dairy products, and mineral supplements. (7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, PROMACTA may cause fetal harm.
- 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 chronic ITP patients with hepatic impairment. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2012

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. PROMACTA, in combination with interferon and ribavirin in patients with chronic hepatitis C, may increase the risk of hepatic decompensation *[see Warnings and Precautions (5.1, 5.2)]***.**

- **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) in patients with normal liver function or ≥3X baseline in patients with pre-treatment elevations in transaminases 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.**

1 INDICATIONS AND USAGE

1.1 Treatment of Thrombocytopenia in Patients with Chronic ITP

PROMACTA® is indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

1.2 Treatment of Thrombocytopenia in Patients with Hepatitis C Infection

PROMACTA is indicated for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy.

1.3 Limitations of use

- PROMACTA should not be used to normalize platelet counts.
- PROMACTA should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding.
- PROMACTA should be used only in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy.
- Safety and efficacy have not been established in combination with direct acting antiviral agents approved for treatment of chronic hepatitis C genotype 1 infection.

2 DOSAGE AND ADMINISTRATION

2.1 Chronic Immune (Idiopathic) Thrombocytopenia

Use the lowest dose of PROMACTA to achieve and maintain a platelet count greater than or equal to 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 to normalize platelet counts *[see Warnings and Precautions (5.4)]*. 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)]*.

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 ITP patients of East Asian ancestry, initiate PROMACTA at a reduced dose of 25 mg once daily *[see Use in Specific Populations (8.8) and Clinical Pharmacology (12.3)]*.

For ITP 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) and Clinical Pharmacology (12.3)]*.

For ITP patients of East Asian ancestry with hepatic impairment (Child-Pugh Class A, B, C), consider initiating PROMACTA at a reduced dose of 12.5 mg once daily *[see Clinical Pharmacology (12.3)]*.

Monitoring and Dose Adjustment: After initiating PROMACTA, adjust the dose to achieve and maintain a platelet count greater than or equal to 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 with differentials (including platelet counts) weekly until a stable platelet count has been achieved. Obtain CBCs with differentials (including platelet counts) monthly thereafter.

Table 1. Dose Adjustments of PROMACTA in Adults With Chronic Immune (Idiopathic) Thrombocytopenia

Platelet Count Result	Dose Adjustment or Response
$<50 \times 10^9$/L following at least 2 weeks of PROMACTA	Increase daily dose by 25 mg to a maximum of 75 mg/day. For patients taking 12.5 mg once daily, increase the dose to 25 mg daily before increasing the dose amount by 25 mg.
$\geq 200 \times 10^9$/L to $\leq 400 \times 10^9$/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.
$>400 \times 10^9$/L	Stop PROMACTA; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is $<150 \times 10^9$/L, reinitiate therapy at a daily dose reduced by 25 mg. For patients taking 25 mg once daily, reinitiate therapy at a daily dose of 12.5 mg.
$>400 \times 10^9$/L after 2 weeks of therapy at lowest dose of PROMACTA	Discontinue PROMACTA.

In ITP 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.

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)]*.

2.2 Chronic Hepatitis C-Associated Thrombocytopenia

Use the lowest dose of PROMACTA to achieve and maintain a platelet count necessary to initiate and maintain antiviral therapy with pegylated interferon and ribavirin. Dose adjustments are based upon the platelet count response. Do not use PROMACTA to normalize platelet counts *[see Warnings and Precautions (5.4)]*. In clinical studies, platelet counts generally began to rise within the first week of treatment with PROMACTA.

Initial Dose Regimen: Initiate PROMACTA at a dose of 25 mg once daily.

Monitoring and Dose Adjustment: Adjust the dose of PROMACTA in 25 mg increments every 2 weeks as necessary to achieve the target platelet count required to initiate antiviral therapy. Monitor platelet counts every week prior to starting antiviral therapy.

During antiviral therapy, adjust the dose of PROMACTA to avoid dose reductions of peginterferon. Monitor CBCs with differentials (including platelet counts) weekly during

antiviral therapy until a stable platelet count is achieved. Monitor platelet counts monthly thereafter. Do not exceed a dose of 100 mg daily. Monitor clinical hematology and liver tests regularly throughout therapy with PROMACTA.

For specific dosage instructions for peginterferon or ribavirin, refer to their respective prescribing information.

Table 2. Dose Adjustments of PROMACTA in Adults With Chronic Hepatitis C

Platelet Count Result	Dose Adjustment or Response
$<50 \times 10^9$/L following at least 2 weeks of PROMACTA	Increase daily dose by 25 mg to a maximum of 100 mg/day.
$\geq 200 \times 10^9$/L to $\leq 400 \times 10^9$/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.
$>400 \times 10^9$/L	Stop PROMACTA; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is $<150 \times 10^9$/L, reinitiate therapy at a daily dose reduced by 25 mg. For patients taking 25 mg once daily, reinitiate therapy at a daily dose of 12.5 mg.
$>400 \times 10^9$/L after 2 weeks of therapy at lowest dose of PROMACTA	Discontinue PROMACTA.

Discontinuation:

The prescribing information for pegylated interferon and ribavirin include recommendations for antiviral treatment discontinuation for treatment futility. Refer to pegylated interferon and ribavirin prescribing information for discontinuation recommendations for antiviral treatment futility.

PROMACTA should be discontinued when antiviral therapy is discontinued. Excessive platelet count responses, as outlined in Table 2, or important liver test abnormalities also necessitate discontinuation of PROMACTA *[see Warnings and Precautions (5.1)]*.

2.3 Administration

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)]*.

3 DOSAGE FORMS AND STRENGTHS

- 12.5 mg tablets — round, biconvex, white, film-coated tablets debossed with GS MZ1 and 12.5 on one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to 12.5 mg of eltrombopag free acid.
- 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 FFS and 75 on one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to 75 mg of eltrombopag free acid.
- 100 mg tablets — round, biconvex, green, film-coated tablets debossed with GS 1L5 and 100 on one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to 100 mg of eltrombopag free acid.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

PROMACTA may cause hepatotoxicity. In the controlled clinical studies in chronic ITP, 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 chronic ITP 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 trial. Six of these patients again experienced liver test abnormalities (predominantly Grade 1) resulting in discontinuation of PROMACTA in one patient. In the extension chronic ITP trial, one additional patient had PROMACTA discontinued due to liver test abnormalities (≤Grade 3).

In 2 controlled clinical studies in patients with chronic hepatitis C and thrombocytopenia, ALT or AST ≥3X ULN was reported in 34% and 38% of the PROMACTA and placebo groups, respectively. Most patients receiving PROMACTA in combination with peginterferon/ribavirin therapy will experience indirect hyperbilirubinemia. Overall, total bilirubin ≥1.5 X ULN was reported in 76% and 50% of patients receiving PROMACTA and placebo, respectively.

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 ULN in patients with normal liver function or ≥3X baseline in patients with pre-treatment elevations in transaminases 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.

5.2 Hepatic Decompensation in Patients with Chronic Hepatitis C

Chronic hepatitis C patients with cirrhosis may be at risk of hepatic decompensation and death when treated with alfa interferons. In 2 controlled clinical trials in patients with chronic hepatitis C and thrombocytopenia, ascites and encephalopathy were reported more frequently for PROMACTA (7%) than placebo (4%). Patients with low albumin levels (<3.5 g/dL) or Model for End-Stage Liver Disease (MELD) score ≥10 at baseline had a greater risk of hepatic decompensation. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation. Refer to alfa interferon prescribing information for discontinuation recommendations. PROMACTA should be discontinued if antiviral therapy is discontinued for hepatic decompensation.

5.3 Bone Marrow Reticulin Formation and Risk for Bone Marrow Fibrosis

PROMACTA may increase the risk for development or progression of reticulin fiber deposition within the bone marrow. In the extension trial in chronic ITP, 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 pre-existing MF Grade 1 developed a MF Grade 2 and subsequently discontinued treatment with PROMACTA. Clinical studies have not demonstrated clinical consequences to date. If new or worsening blood morphological abnormalities or cytopenias occur, consider a bone marrow biopsy including staining for fibrosis.

5.4 Thrombotic/Thromboembolic Complications

In 2 controlled clinical trials in patients with chronic hepatitis C and thrombocytopenia, 3% (31/955) treated with PROMACTA experienced a thrombotic event compared to 1% (5/484)

on placebo. The majority of events were of the portal venous system (1% in patients treated with PROMACTA versus <1% for placebo).

Thrombotic/thromboembolic complications may result from increases in platelet counts with PROMACTA. Reported thrombotic/thromboembolic complications included both venous and arterial events and were observed at low and at normal platelet counts.

Consider the potential for an increased risk of thromboembolism 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 target platelet counts *[see Dosage and Administration (2.1, 2.2)]*.

In a controlled trial 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 portal vein thrombosis (PVT). Symptoms of PVT included abdominal pain, nausea, vomiting, and diarrhea. 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.

5.5 Laboratory Monitoring

Complete Blood Counts (CBCs): Obtain CBCs with differentials (including platelet counts) weekly during the dose adjustment phase of therapy with PROMACTA and then monthly following establishment of a stable dose of PROMACTA. Obtain CBCs with differentials (including platelet counts) weekly for at least 4 weeks following discontinuation of PROMACTA. *[See Dosage and Administration (2.1, 2.2) and Warnings and Precautions (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. PROMACTA inhibits UGT1A1 and OATP1B1, which may lead to indirect hyperbilirubinemia. 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)]*.

5.6 Cataracts

In the 3 controlled clinical trials in chronic ITP, cataracts developed or worsened in 15 (7%) patients who received 50 mg PROMACTA daily and 8 (7%) placebo-group patients. In the

extension trial, cataracts developed or worsened in 4% of patients who underwent ocular examination prior to therapy with PROMACTA. In the 2 controlled clinical trials in patients with chronic hepatitis C and thrombocytopenia, cataracts developed or worsened in 8% patients treated with PROMACTA and 5% patients treated with placebo.

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.

6 ADVERSE REACTIONS

The following serious adverse reactions associated with PROMACTA are described in other sections.

- Hepatotoxicity *[see Warnings and Precautions (5.1)]*
- Hepatic Decompensation in Patients With Chronic Hepatitis C *[see Warnings and Precautions (5.2)]*
- Bone Marrow Reticulin Formation and Risk for Bone Marrow Fibrosis *[see Warnings and Precautions (5.3)]*
- Thrombotic/Thromboembolic Complications *[see Warnings and Precautions (5.4)]*
- Cataracts *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

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.

Chronic Immune (Idiopathic) Thrombocytopenic: 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 exposure of PROMACTA 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.

Table 3 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 3. Adverse Reactions (≥3%) from Three Placebo-Controlled Studies in Adults With Chronic Immune (Idiopathic) Thrombocytopenia

Adverse Reaction	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 chronic ITP 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 trial, the adverse reactions occurred in a pattern similar to that seen in the placebo-controlled studies. Table 4 presents the most common treatment-related adverse reactions (experienced by ≥3% of patients receiving PROMACTA) from the extension trial.

Table 4. Treatment-Related Adverse Reactions (≥3%) from Extension Trial in Adults With Chronic Immune (Idiopathic) Thrombocytopenia

Adverse Reaction	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 PROMACTA in non-ITP thrombocytopenic patients with chronic liver disease, six patients in the PROMACTA group and one patient in the placebo group developed portal vein thromboses *[see Warnings and Precautions (5.3)]*.

Chronic Hepatitis C-Associated Thrombocytopenia: In the 2 placebo-controlled trials, 955 patients with chronic hepatitis C-associated thrombocytopenia received PROMACTA. Table 5 presents the most common adverse drug reactions (experienced by ≥10% of patients receiving PROMACTA compared to placebo).

Table 5. Adverse Reactions (≥10% and Greater than Placebo) from Two Placebo-Controlled Studies in Adults With Chronic Hepatitis C

Adverse Reaction	PROMACTA + Peginterferon/ Ribavirin n = 955 (%)	Placebo + Peginterferon/Ribavirin n = 484 (%)
Anemia	40	35
Pyrexia	30	24
Fatigue	28	23
Headache	21	20
Nausea	19	14
Diarrhea	19	11
Decreased appetite	18	14
Influenza-like illness	18	16
Asthenia	16	13
Insomnia	16	15
Cough	15	12
Pruritus	15	13
Chills	14	9
Myalgia	12	10
Alopecia	10	6
Peripheral edema	10	5

In the 2 controlled clinical studies in patients with chronic hepatitis C, hyperbilirubinemia was also reported (8% for PROMACTA versus 3% for placebo).

7 DRUG INTERACTIONS

In vitro, CYP1A2, CYP2C8, UDP-glucuronosyltransferase (UGT)1A1 and UGT1A3 are involved in the metabolism of eltrombopag. In vitro, eltrombopag inhibits the following metabolic or transporter systems: CYP2C8, CYP2C9, UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, UGT2B15, OATP1B1 and breast cancer resistance protein (BCRP) *[see Clinical Pharmacology (12.3)]*.

7.1 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 trial, administration of PROMACTA with a polyvalent cation-containing antacid decreased plasma eltrombopag systemic exposure by approximately 70% *[see Clinical Pharmacology (12.3)]*.

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)]*.

7.2 Transporters

Co-administration of PROMACTA with the OATP1B1 and BCRP substrate, rosuvastatin, to healthy adult subjects increased plasma rosuvastatin $AUC_{0-\infty}$ by 55% and C_{max} by 103% *[see Clinical Pharmacology (12.3)]*.

Use caution when concomitantly administering PROMACTA and drugs that are substrates of OATP1B1 [e.g., atorvastatin, bosentan, ezetimibe, fluvastatin, glyburide, olmesartan, pitavastatin, pravastatin, rosuvastatin, repaglinide, rifampin, simvastatin acid, SN-38 (active metabolite of irinotecan), valsartan] or BCRP (e.g., imatinib, irinotecan, lapatinib, methotrexate, mitoxantrone, rosuvastatin, sulfasalazine, topotecan). 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 PROMACTA, a dose reduction of rosuvastatin by 50% was recommended.

7.3 Lopinavir/ritonavir

In a drug interaction study, co-administration of PROMACTA with lopinavir/ritonavir (LPV/RTV) decreased plasma eltrombopag exposure by 17% *[see Clinical Pharmacology (12.3)]*. No dose adjustment is recommended when PROMACTA is co-administered with LPV/RTV. Drug interactions with other HIV protease inhibitors have not been evaluated.

7.4 Peginterferon Alfa 2a/b Therapy

Co-administration of peginterferon alfa 2a (PEGASYS®) or 2b (PEGINTRON®) did not affect eltrombopag exposure in 2 randomized, double-blind, placebo-controlled trials with adult patients with chronic hepatitis C.

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, respectively, the human clinical exposure based on AUC in ITP patients at 75 mg/day and 0.3, 1, and 3 times, respectively, the human clinical exposure based on AUC in chronic hepatitis C patients at 100 mg/day). 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, respectively, the human clinical exposure based on AUC in ITP patients at 75 mg/day and 0.3, 1, and 3 times, respectively, the human clinical exposure based on AUC in chronic hepatitis C patients at 100 mg/day). 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, respectively, the human clinical exposure based on AUC in ITP patients at 75 mg/day and 0.02, 0.1, and 0.3 times, respectively, the human clinical exposure based on AUC in chronic hepatitis C patients at 100 mg/day). 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 in ITP patients at 75 mg/day and similar to the human clinical exposure based on AUC in chronic hepatitis C patients at 100 mg/day). 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 in chronic ITP, 22% were 65 years of age and over, while 9% were 75 years of age and over. In the 2 randomized clinical trials of PROMACTA in patients with chronic hepatitis C and thrombocytopenia, 7% were 65 years of age and over, while fewer than 1% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these patients and younger patients in the placebo-controlled studies, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

Hepatic impairment influences the exposure of PROMACTA *[see Clinical Pharmacology (12.3)]*.

A reduction in the initial dose of PROMACTA in patients with chronic ITP 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)]. No dosage adjustment is necessary for HCV patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No adjustment in the initial PROMACTA dose is needed for patients with renal impairment *[see Clinical Pharmacology (12.3)]*. Closely monitor patients with impaired renal function when administering PROMACTA.

8.8 Ethnicity

Patients of East Asian ethnicity (i.e., Japanese, Chinese, Taiwanese, and Korean) exhibit higher eltrombopag exposures. A reduction in the initial dose of PROMACTA is recommended for ITP patients of East Asian ancestry and patients of East Asian ancestry with hepatic impairment (Child-Pugh Class A, B, C) *[see Dosage and Administration (2.1)]*. No dose reduction is needed in patients of East Asian ethnicity with chronic hepatitis C *[see Clinical Pharmacology (12.3)]*.

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.

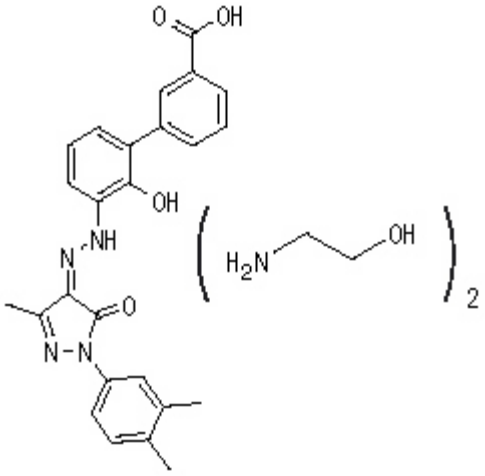
In case of an overdose, consider oral administration of a metal cation-containing preparation, such as calcium, aluminum, or magnesium preparations to chelate eltrombopag and thus limit absorption. Closely monitor platelet counts. Reinitiate treatment with PROMACTA in accordance with dosing and administration 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 12.5 mg, 25 mg, 50 mg, 75 mg, or 100 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, polysorbate 80 (12.5 mg tablet), FD&C Yellow No. 6 aluminum lake (25 mg tablet), FD&C Blue No. 2 aluminum lake (50 mg tablet), Iron Oxide Red and Iron Oxide Black (75 mg tablet), or Iron Oxide Yellow and Iron Oxide Black (100 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

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 trial 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.

Drug Interactions: *Polyvalent Cation-containing Antacids:* In a clinical trial, co-administration of 75 mg of PROMACTA with a polyvalent cation-containing antacid (1,524 mg aluminum hydroxide, 1,425 mg magnesium carbonate, and sodium alginate) to 26 healthy adult subjects decreased plasma eltrombopag $AUC_{0-\infty}$ and C_{max} by approximately 70%. The contribution of sodium alginate to this interaction is not known.

Cytochrome P450 Enzymes (CYPs): In a clinical trial, 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 trial.

Rosuvastatin: In a clinical trial, co-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%.

Lopinavir/Ritonavir: In a clinical trial, co-administration of repeat dose lopinavir 400 mg /ritonavir 100 mg twice daily with a single dose of PROMACTA 100 mg to 40 healthy adult subjects decreased plasma eltrombopag $AUC_{0-\infty}$ by 17%.

Pegylated Interferon alfa-2a + Ribavirin and Pegylated Interferon alfa-2b + Ribavirin: The pharmacokinetics of eltrombopag in both the presence and absence of pegylated interferon alfa 2a and 2b therapy were evaluated using a population pharmacokinetic analysis in 635 patients with chronic hepatitis C. The population PK model estimates of clearance indicate no significant difference in eltrombopag clearance in the presence of pegylated interferon alfa plus ribavirin therapy.

In vitro Studies: Eltrombopag is an inhibitor of CYP2C8 and CYP2C9 *in vitro*. Eltrombopag is an inhibitor of UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15 *in vitro*. Eltrombopag is an inhibitor of the organic anion transporting polypeptide OATP1B1 and BCRP *in vitro*.

Specific Populations: *Ethnicity:* Based on two population PK analyses of eltrombopag concentrations in ITP and chronic hepatitis C patients, East Asian (i.e., Japanese, Chinese, Taiwanese, and Korean) subjects exhibited 50 to 55% higher eltrombopag plasma concentrations compared to non-East Asian subjects *[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 trial. The effect of African-American ethnicity on exposure and related safety and efficacy of eltrombopag has not been established.

Hepatic Impairment: In a pharmacokinetic trial, the disposition of a single 50 mg dose of PROMACTA 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 Class A) compared to subjects with normal hepatic function. Plasma eltrombopag $AUC_{0-\infty}$ was approximately 2-fold higher in patients with moderate (Child-Pugh Class B) and severe hepatic impairment (Child-Pugh Class C). The half-life of eltrombopag was prolonged 2-fold in these patients. This clinical trial did not evaluate protein binding effects.

Chronic Liver Disease: A population PK analysis in thrombocytopenic patients with chronic liver disease following repeat doses of eltrombopag 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 compared to patients with normal hepatic function. The half-life of eltrombopag was prolonged 3-fold in patients with mild hepatic impairment and 4-fold in patients with moderate hepatic impairment. This clinical trial did not evaluate protein binding effects.

Chronic Hepatitis C: A population PK in 28 healthy adults and 635 patients with chronic hepatitis C demonstrated that patients with chronic hepatitis C treated with PROMACTA had higher plasma $AUC_{(0-\tau)}$ values as compared to healthy subjects, and $AUC_{(0-\tau)}$ increased with increasing Child-Pugh score. Patients with chronic hepatitis C and mild hepatic impairment had approximately 100% to 144% higher plasma $AUC_{(0-\tau)}$ compared with healthy subjects. This clinical trial did not evaluate protein binding effects.

Renal Impairment: The disposition of a single 50 mg dose of PROMACTA in patients with mild (creatinine clearance (CrCl) of 50 to 80 mL/min), moderate (CrCl of 30 to 49 mL/min), and severe (CrCl less than 30 mL/min) 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.

12.6 Assessment of Risk of 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 in ITP patients at 75 mg/day and 2 times the human clinical exposure based on AUC in chronic hepatitis C patients at 100 mg/day).

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 ITP patients at 75 mg/day and 7 times the human clinical exposure based on C_{max} in chronic hepatitis C patients at 100 mg/day). 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 in ITP patients at 75 mg/day and similar to the human clinical exposure based on AUC in chronic hepatitis C patients at 100 mg/day). 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 in ITP patients at 75 mg/day and 2 times the human clinical exposure based on AUC in chronic hepatitis C patients at 100 mg/day).

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 in ITP patients at 75 mg/day and 3 times the human clinical exposure based on AUC in chronic hepatitis C patients at 100 mg/day, 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 in ITP patients at 75 mg/day and 2 times the human clinical exposure based on AUC in chronic hepatitis C patients at 100 mg/day, cataracts were observed in mice after 13 weeks and in rats after 39 weeks of dosing *[see Warnings and Precautions (5.6)]*.

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 in ITP patients at 75 mg/day and 0.6 times the human clinical exposure based on AUC in chronic hepatitis C patients at 100 mg/day. 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

14.1 Chronic ITP

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

Trials 1 and 2: In trials 1 and 2, patients who had completed at least one prior ITP therapy and who had a platelet count <30 x 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 trials, PROMACTA or placebo was discontinued if the platelet count exceeded 200 x 10^9/L. The primary efficacy endpoint was response rate, defined as a shift from a baseline platelet count of <30 x 10^9/L to ≥50 x 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 x 10^9/L) were similar among all treatment groups.

Trial 1 randomized 114 patients (2:1) to PROMACTA 50 mg or placebo. Trial 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 6 shows for each trial the primary efficacy outcomes for the placebo groups and the patient groups who received the 50 mg daily regimen of PROMACTA.

Table 6. Trials 1 and 2 Platelet Count Response (≥50 x 10^9/L) Rates in Adults With Chronic Immune (Idiopathic) Thrombocytopenia

Trial	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 trial 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 Trial 1 and 43 days in Trial 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.

Trial 3: In this trial, 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 trial as clinically indicated. The primary endpoint was the odds of achieving a platelet count $\geq 50 \times 10^9$/L and $\leq 400 \times 10^9$/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 $\leq 15 \times 10^9$/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 $\geq 50 \times 10^9$/L and $\leq 400 \times 10^9$/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 50×10^9/L and 400×10^9/L during the entire 6-month treatment period compared to those patients treated with placebo.

Outcomes of treatment are presented in Table 7 for all patients enrolled in the trial.

Table 7. Outcomes of Treatment from Trial 3 in Adults With Chronic Immune (Idiopathic) Thrombocytopenia

Outcome	**PROMACTA N = 135**	**Placebo N = 62**
Mean number of weeks with platelet counts $\geq 50 \times 10^9$/L	11.3	2.4
Requiring rescue therapy, n (%)	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 trial.

Extension Trial: Patients who completed any prior clinical trial with PROMACTA were enrolled in an open-label, single-arm trial 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 19 x 10^9/L prior to administration of PROMACTA.

14.2 Chronic Hepatitis C-Associated Thrombocytopenia

The efficacy and safety of PROMACTA for the treatment of thrombocytopenia in adult patients with chronic hepatitis C were evaluated in 2 randomized, double-blind, placebo-controlled trials. Trial 1 utilized peginterferon alfa-2a (PEGASYS®) plus ribavirin for antiviral treatment and Trial 2 utilized peginterferon alfa-2b (PEGINTRON®) plus ribavirin. In both trials, patients with a platelet count of <75 x 10^9/L were enrolled and stratified by platelet count, screening HCV RNA, and HCV genotype. Patients were excluded if they had evidence of decompensated liver disease with Child-Pugh score > 6 (class B and C), history of ascites, or hepatic encephalopathy. The median age of the patients in both trials was 52 years, 63% were male, and 74% were Caucasian. Sixty-nine percent of patients had HCV genotypes 1, 4, 6 with the remainder genotypes 2 and 3. Approximately 30% of patients had been previously treated with interferon and ribavirin. The majority of patients (90%) had bridging fibrosis and cirrhosis, as indicated by noninvasive testing. A similar proportion (95%) of patients in both treatment groups had Child-Pugh level A (score 5-6) at baseline. A similar proportion of patients (2%) in both treatment groups had baseline international normalized ratio (INR) > 1.7. Median baseline platelet counts (approximately 60 x 10^9/L) were similar in both treatment groups. The trials consisted of two phases – a pre-antiviral treatment phase and an antiviral treatment phase. In the pre-antiviral treatment phase, patients received open-label PROMACTA to increase the platelet count to a threshold of ≥90 x 10^9/L for Trial 1 and ≥100 x 10^9/L for Trial 2. PROMACTA was administered at an initial dose of 25 mg once daily for 2 weeks and increased in 25 mg increments over 2 to 3 week periods to achieve the optimal platelet count to initiate antiviral therapy. The maximal time patients could receive open-label PROMACTA was 9 weeks. If threshold platelet counts were achieved, patients were randomized (2:1) to the same dose of PROMACTA at the end of the pre-treatment phase or to placebo. PROMACTA was administered in combination with pegylated interferon and ribavirin per their respective prescribing information for up to 48 weeks.

The primary efficacy endpoint for both trials was sustained virologic response (SVR) defined as the percentage of patients with undetectable HCV-RNA at 24 weeks after completion of antiviral treatment. The median time to achieve the target platelet count ≥90 x 10^9/L was approximately 2 weeks. Ninety-five percent of patients were able to initiate antiviral therapy.

In both trials, a significantly greater proportion of patients treated with PROMACTA achieved SVR (see Table 8). The improvement in the proportion of patients who achieved SVR was consistent across subgroups based on baseline platelet count (<50 x 10^9/L versus ≥50 x 10^9/L). In patients with high baseline viral loads (≥800,000), the SVR rate was 18% (82/452) for PROMACTA versus 8% (20/239) for placebo.

Table 8. Trials 1 and 2 Sustained Virologic Response in Adults With Chronic Hepatitis C

	Trial 1[a]		**Trial 2[b]**	
Pre-antiviral Treatment Phase	N = 715		N = 805	
% Patients who achieved target platelet counts and initiated antiviral therapy[c]	95%		94%	
Antiviral Treatment Phase	**PROMACTA N = 450 %**	**Placebo N = 232 %**	**PROMACTA N = 506 %**	**Placebo N = 253 %**
Overall SVR[d]	23	14	19	13
HCV Genotype 2,3	35	24	34	25
HCV Genotype 1,4,6	18	10	13	7

[a] PROMACTA given in combination with peginterferon alfa-2a (180 mcg once weekly for 48 weeks for genotypes 1/4/6; 24 weeks for genotype 2 or 3) plus ribavirin (800 to 1,200 mg daily in 2 divided doses orally).

[b] PROMACTA given in peginterferon alfa-2b (1.5 mcg/kg once weekly for 48 weeks for genotypes 1/4/6; 24 weeks for genotype 2 or 3) plus ribavirin (800 to 1,400 mg daily in 2 divided doses orally).

[c] Target platelet count was $\geq 90 \times 10^9$/L for Trial 1 and $\geq 100 \times 10^9$/L for Trial 2.

[d] *P* value <0.05 for PROMACTA versus placebo.

The majority of patients treated with PROMACTA (76%) maintained a platelet count $\geq 50 \times 10^9$/L compared to 19% for placebo. A greater proportion of patients on PROMACTA did not require any antiviral dose reduction as compared to placebo (45% versus 27%).

16 HOW SUPPLIED/STORAGE AND HANDLING

- The 12.5 mg tablets are round, biconvex, white, film-coated tablets debossed with GS MZ1 and 12.5 on one side and are available in bottles of 30: NDC 0007-4643-13.
- 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.
- The 100 mg tablets are round, biconvex, green, film-coated tablets debossed with GS 1L5 and 100 on one side and are available in bottles of 30: NDC 0007-4644-13. This product contains a dessicant.

Store at room temperature between 20°C and 25°C (68°F to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not remove desiccant if present. Dispense in original bottle.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Prior to treatment, patients should fully understand and be informed of the following risks and considerations for PROMACTA:

- For patients with ITP, 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,
- For patients with chronic hepatitis C, therapy with PROMACTA is administered to achieve and maintain a platelet count necessary to initiate and maintain antiviral therapy with pegylated interferon and ribavirin.
- Therapy with PROMACTA may be associated with hepatobiliary laboratory abnormalities.
- Advise patients with chronic hepatitis C and cirrhosis that they may be at risk for hepatic decompensation when receiving alfa interferon therapy.
- Advise 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
- Advise patients that thrombocytopenia and risk of bleeding may reoccur upon discontinuing PROMACTA, particularly if PROMACTA is discontinued while the patient is on anticoagulants or antiplatelet agents.
- Advise patients that too much PROMACTA may result in excessive platelet counts and a risk for thrombotic/thromboembolic complications.
- Advise patients that during therapy with PROMACTA, they should continue to avoid situations or medications that may increase the risk for bleeding.
- Advise patients to have a baseline ocular examination prior to administration of PROMACTA and be monitored for signs and symptoms of cataracts during therapy.
- Advise patients 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.

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GlaxoSmithKline
Research Triangle Park, NC 27709

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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
  - confusion
  - swelling of the stomach area (abdomen)

Your risk of developing liver problems may be increased if you have chronic hepatitis C virus with cirrhosis, and take PROMACTA with interferon and ribavirin treatment.

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) thrombocytopenia (ITP), when other medicines to treat your ITP or surgery to remove the spleen have not worked well enough.

- chronic hepatitis C virus (HCV) infection before and during treatment with interferon.

PROMACTA is used to try to raise your platelet count in order to lower your risk for bleeding.

PROMACTA is not used to make your platelet count normal.

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

It is not known if PROMACTA is safe and effective when used with other antiviral medicines which are approved to treat chronic hepatitis C.

It is not known if PROMACTA is safe and effective in children.

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
- 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 or plan to become 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 breastfeeding or plan to breastfeed. It is not known if PROMACTA passes into your breast milk. You and your healthcare provider should decide whether

you will take PROMACTA or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. 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?

- Take PROMACTA exactly as your healthcare provider tells you. Do not stop taking 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 risk 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, including:

- See **"What is the most important information I should know about PROMACTA?"**
- **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.
- **High platelet counts and higher risk for blood clots.** Your risk of getting a blood clot is increased if your platelet count is too high during treatment with PROMACTA. Your risk 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 problems 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.
  People 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.
- **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.

The most common side effects of PROMACTA when used to treat chronic ITP 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 people, pain or burning with urination
- pain or swelling (inflammation) in your throat or mouth (oropharyngeal pain and pharyngitis)
- abnormal liver function tests
- back pain
- “flu” like symptoms (influenza) including fever, headache, tiredness, cough, sore throat, and body aches
- skin tingling, itching, or burning
- rash

The most common side effects when PROMACTA is used in combination with other medicines to treat chronic HCV are:

- low red blood cell count (anemia)
- fever
- tiredness
- headache
- nausea
- diarrhea
- decreased appetite
- “flu” like symptoms (influenza) including fever, headache, tiredness, cough, sore throat, and body aches
- feeling weak
- trouble sleeping
- cough
- itching
- chills
- muscle aches
- hair loss
- swelling in your ankles, feet, and legs

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of PROMACTA. 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 68°F to 77°F (20°C to 25°C).
- Keep PROMACTA tightly closed in the bottle given to you.
- The PROMACTA bottle may contain a desiccant pack to help keep your medicine dry. Do not remove the desiccant pack from the bottle.
- **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, polysorbate 80 (12.5 mg tablet), and FD&C Yellow No. 6 aluminum lake (25 mg tablet), FD&C Blue No. 2 aluminum lake (50 mg tablet), Iron Oxide Red and Iron Oxide Black (75 mg tablet), or Iron Oxide Yellow and Iron Oxide Black (100 mg tablet).

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

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GlaxoSmithKline
Research Triangle Park, NC 27709

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