

## 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  $\geq 3X$  upper limit of normal (ULN) and are:
  - progressive, or
  - persistent for  $\geq 4$  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, PROMACTA Distribution Program removal	12/2011
Dosage and Administration, PROMACTA Distribution Program removal (2)	12/2011
Dosage and Administration, Initial Dose Regimen (2.1)	12/2011
Dosage and Administration, Monitoring and Dose Adjustment (2.2)	12/2011
Warnings and Precautions, Bone Marrow Reticulin Formation (5.2)	12/2011
Warnings and Precautions, Thrombotic/Thromboembolic Complications (5.3)	02/2011
Warnings and Precautions, Recurrence of Thrombocytopenia and Hemorrhage Risk After Cessation of PROMACTA removal (formerly 5.3)	12/2011
Warnings and Precautions, PROMACTA Distribution Program removal (formerly 5.8)	12/2011

### 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)

Limitations of use:

- PROMACTA should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding. (1)
- 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)
- Adjust the daily dose to achieve and maintain a platelet count  $\geq 50 \times 10^9/L$  in order to reduce the risk for bleeding. (2)
- Do not exceed a daily dose of 75 mg. (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)
- 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

12.5 mg, 25 mg, 50 mg, and 75 mg tablets. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to 12.5 mg, 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)
- Thrombotic/thromboembolic complications may result from increases in platelet counts with PROMACTA. Portal vein thrombosis has been reported in patients with chronic liver disease receiving PROMACTA. Monitor platelet counts regularly. (5.3)
- Monitor 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. (5.5)

### ADVERSE REACTIONS

The most common adverse reactions (occurring in  $\geq 3\%$  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](http://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. (7.4)

### 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: 12/2011

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### WARNING: RISK FOR HEPATOTOXICITY

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

- 2.1 Initial Dose Regimen
- 2.2 Monitoring and Dose Adjustment
- 2.3 Discontinuation

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

- 5.1 Risk for Hepatotoxicity
- 5.2 Bone Marrow Reticulin Formation and Risk for Bone Marrow Fibrosis
- 5.3 Thrombotic/Thromboembolic Complications
- 5.4 Hematologic Malignancies
- 5.5 Laboratory Monitoring

- 5.6 Cataracts
- 6 ADVERSE REACTIONS**
  - 6.1 Clinical Trials Experience
- 7 DRUG INTERACTIONS**
  - 7.1 Cytochrome P450
  - 7.2 Transporters
  - 7.3 UDP-glucuronosyltransferases (UGTs)
  - 7.4 Polyvalent Cations (Chelation)
- 8 USE IN SPECIFIC POPULATIONS**
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers
  - 8.4 Pediatric Use
  - 8.5 Geriatric Use
  - 8.6 Hepatic Impairment
  - 8.7 Renal Impairment

- 10 OVERDOSAGE**
- 11 DESCRIPTION**
- 12 CLINICAL PHARMACOLOGY**
  - 12.1 Mechanism of Action
  - 12.3 Pharmacokinetics
  - 12.6 QT/QTc Prolongation
- 13 NONCLINICAL TOXICOLOGY**
  - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
  - 13.2 Animal Pharmacology/Toxicology
- 14 CLINICAL STUDIES**
  - 14.1 Studies 1 and 2
  - 14.2 Study 3
  - 14.3 Extension Study
- 16 HOW SUPPLIED/STORAGE AND HANDLING**
- 17 PATIENT COUNSELING INFORMATION**
  - 17.1 Information for Patients

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

---

## FULL PRESCRIBING INFORMATION

### 1 **WARNING: RISK FOR HEPATOTOXICITY**

2 **PROMACTA may cause hepatotoxicity:**

- 3 ● **Measure serum alanine aminotransferase (ALT), aspartate aminotransferase (AST),**  
4 **and bilirubin prior to initiation of PROMACTA, every 2 weeks during the dose**  
5 **adjustment phase, and monthly following establishment of a stable dose. If bilirubin**  
6 **is elevated, perform fractionation.**
- 7 ● **Evaluate abnormal serum liver tests with repeat testing within 3 to 5 days. If the**  
8 **abnormalities are confirmed, monitor serum liver tests weekly until the**  
9 **abnormality(ies) resolve, stabilize, or return to baseline levels.**
- 10 ● **Discontinue PROMACTA if ALT levels increase to  $\geq 3X$  the upper limit of normal**  
11 **(ULN) and are:**
  - 12 ● **progressive, or**
  - 13 ● **persistent for  $\geq 4$  weeks, or**
  - 14 ● **accompanied by increased direct bilirubin, or**
  - 15 ● **accompanied by clinical symptoms of liver injury or evidence for hepatic**  
16 **decompensation.**

### 17 **1 INDICATIONS AND USAGE**

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

21 Limitations of use: PROMACTA should be used only in patients with ITP whose degree  
22 of thrombocytopenia and clinical condition increases the risk for bleeding. PROMACTA should  
23 not be used in an attempt to normalize platelet counts.

### 24 **2 DOSAGE AND ADMINISTRATION**

25 Use the lowest dose of PROMACTA to achieve and maintain a platelet count  $\geq 50 \times$   
26  $10^9/L$  as necessary to reduce the risk for bleeding. Dose adjustments are based upon the platelet  
27 count response. Do not use PROMACTA in an attempt to normalize platelet counts [*see*  
28 *Warnings and Precautions (5.3)*]. In clinical studies, platelet counts generally increased within 1  
29 to 2 weeks after starting PROMACTA and decreased within 1 to 2 weeks after discontinuing  
30 PROMACTA [*see Clinical Studies (14)*].

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

36 **2.1 Initial Dose Regimen**

37 Initiate PROMACTA at a dose of 50 mg once daily, except in patients who are of East  
38 Asian ancestry (such as Chinese, Japanese, Taiwanese, or Korean) or who have mild to severe  
39 hepatic impairment (Child-Pugh Class A, B, C).

40 For patients of East Asian ancestry, initiate PROMACTA at a reduced dose of 25 mg  
41 once daily [see *Clinical Pharmacology (12.3)*].

42 For patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B,  
43 C), initiate PROMACTA at a reduced dose of 25 mg once daily [see *Use in Specific Populations*  
44 (8.6)].

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

48 **2.2 Monitoring and Dose Adjustment**

49 After initiating PROMACTA, adjust the dose to achieve and maintain a platelet count  
50  $\geq 50 \times 10^9/L$  as necessary to reduce the risk for bleeding. Do not exceed a dose of 75 mg daily.  
51 Monitor clinical hematology and liver tests regularly throughout therapy with PROMACTA and  
52 modify the dosage regimen of PROMACTA based on platelet counts as outlined in Table 1.  
53 During therapy with PROMACTA, assess CBCs with differentials (including platelet count)  
54 weekly until a stable platelet count has been achieved. Obtain CBCs with differentials (including  
55 platelet counts) monthly thereafter.

56  
57 **Table 1. Dose Adjustments of PROMACTA**

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 $< 150 \times 10^9/L$ , reinstitute therapy at a daily dose reduced by 25 mg. For patients taking 25 mg once daily, reinstitute 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.

58  
59 In patients with hepatic impairment (Child-Pugh Class A, B, C), after initiating  
60 PROMACTA or after any subsequent dosing increase wait 3 weeks before increasing the dose.

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

### 64 **2.3 Discontinuation**

65 Discontinue PROMACTA if the platelet count does not increase to a level sufficient to  
66 avoid clinically important bleeding after 4 weeks of therapy with PROMACTA at the maximum  
67 daily dose of 75 mg. Excessive platelet count responses, as outlined in Table 1, or important liver  
68 test abnormalities also necessitate discontinuation of PROMACTA [*see Warnings and*  
69 *Precautions (5.1)*].

## 70 **3 DOSAGE FORMS AND STRENGTHS**

71 12.5 mg tablets — round, biconvex, white, film-coated tablets debossed with GS MZ1  
72 and 12.5 on one side. Each tablet, for oral administration, contains eltrombopag olamine,  
73 equivalent to 12.5 mg of eltrombopag free acid.

74 25 mg tablets — round, biconvex, orange, film-coated tablets debossed with GS NX3 and  
75 25 on one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to  
76 25 mg of eltrombopag free acid.

77 50 mg tablets — round, biconvex, blue, film-coated tablets debossed with GS UFU and  
78 50 on one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to  
79 50 mg of eltrombopag free acid.

80 75 mg tablets — round, biconvex, pink, film-coated tablets debossed with GS FFS and  
81 75 on one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to  
82 75 mg of eltrombopag free acid.

## 83 **4 CONTRAINDICATIONS**

84 None.

## 85 **5 WARNINGS AND PRECAUTIONS**

### 86 **5.1 Risk for Hepatotoxicity**

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

99 extension study, one additional patient had PROMACTA discontinued due to liver test  
100 abnormalities ( $\leq$ Grade 3).

101 Measure serum ALT, AST, and bilirubin prior to initiation of PROMACTA, every  
102 2 weeks during the dose adjustment phase, and monthly following establishment of a stable dose.  
103 If bilirubin is elevated, perform fractionation. Evaluate abnormal serum liver tests with repeat  
104 testing within 3 to 5 days. If the abnormalities are confirmed, monitor serum liver tests weekly  
105 until the abnormality(ies) resolve, stabilize, or return to baseline levels. Discontinue  
106 PROMACTA if ALT levels increase to  $\geq 3X$  the upper limit of normal (ULN) and are:

- 107 • progressive, or
- 108 • persistent for  $\geq 4$  weeks, or
- 109 • accompanied by increased direct bilirubin, or
- 110 • accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation.

111 Reinitiating treatment with PROMACTA is not recommended. If the potential benefit for  
112 reinitiating treatment with PROMACTA is considered to outweigh the risk for hepatotoxicity,  
113 then cautiously reintroduce PROMACTA and measure serum liver tests weekly during the dose  
114 adjustment phase. If liver tests abnormalities persist, worsen or recur, then permanently  
115 discontinue PROMACTA.

116 Pharmacokinetic evaluations in patients with hepatic impairment show that plasma  
117 eltrombopag  $AUC_{(0-\tau)}$  increases with increasing degree of hepatic impairment (as measured by  
118 Child-Pugh). Exercise caution when administering PROMACTA to patients with hepatic  
119 impairment (Child-Pugh Class A, B, C). Use a lower starting dose of PROMACTA in patients  
120 with any degree of hepatic impairment and monitor closely [*see Dosage and Administration*  
121 (2.1) and *Use in Specific Populations* (8.6)].

## 122 **5.2 Bone Marrow Reticulin Formation and Risk for Bone Marrow Fibrosis**

123 PROMACTA may increase the risk for development or progression of reticulin fiber  
124 deposition within the bone marrow. In the extension study, 151 patients have had bone marrow  
125 biopsies evaluated for increased reticulin and collagen fiber deposition. Bone marrow biopsies  
126 taken after 1 year of therapy showed predominantly myelofibrosis (MF) Grade 1 or less in  
127 140/151 (93%) of patients. There were 11/151 (7%) of patients with MF Grade 2. Four patients  
128 had collagen deposition reported. One patient with a pre-existing MF Grade 1 developed a MF  
129 Grade 2 and subsequently discontinued treatment with PROMACTA. Clinical studies have not  
130 excluded a risk of bone marrow fibrosis with clinical consequences. If new or worsening blood  
131 morphological abnormalities or cytopenias occur, consider a bone marrow biopsy including  
132 staining for fibrosis.

## 133 **5.3 Thrombotic/Thromboembolic Complications**

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

137 Consider the potential for an increased risk of thromboembolism when administering  
138 PROMACTA to patients with known risk factors for thromboembolism (e.g., Factor V Leiden,

139 ATIII deficiency, antiphospholipid syndrome, chronic liver disease). To minimize the risk for  
140 thrombotic/thromboembolic complications, do not use PROMACTA in an attempt to normalize  
141 platelet counts. Follow the dose adjustment guidelines to achieve and maintain a platelet count of  
142  $\geq 50 \times 10^9/L$  as necessary to decrease the risk for bleeding [*see Dosage and Administration*  
143 (2.2)].

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

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

#### 160 **5.4 Hematologic Malignancies**

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

#### 168 **5.5 Laboratory Monitoring**

169 Complete Blood Counts (CBCs): Obtain CBCs with differentials (including platelet  
170 counts) weekly during the dose adjustment phase of therapy with PROMACTA and then  
171 monthly following establishment of a stable dose of PROMACTA. Obtain CBCs (including  
172 platelet counts) weekly for at least 4 weeks following discontinuation of PROMACTA. [*See*  
173 *Dosage and Administration (2) and Warnings and Precautions (5.2)*.]

174 Liver Tests: Monitor serum liver tests (ALT, AST, and bilirubin) prior to initiation of  
175 PROMACTA, every 2 weeks during the dose adjustment phase, and monthly following  
176 establishment of a stable dose. If bilirubin is elevated, perform fractionation. If abnormal levels  
177 are detected, repeat the tests within 3 to 5 days. If the abnormalities are confirmed, monitor  
178 serum liver tests weekly until the abnormality(ies) resolve, stabilize, or return to baseline levels.

179 Discontinue PROMACTA for the development of important liver test abnormalities [*see*  
180 *Warnings and Precautions (5.1)*].

## 181 **5.6 Cataracts**

182 In the 3 controlled clinical studies, cataracts developed or worsened in 15 (7%) patients  
183 who received 50 mg PROMACTA daily and 8 (7%) placebo-group patients. In the extension  
184 study, cataracts developed or worsened in 4% of patients who underwent ocular examination  
185 prior to therapy with PROMACTA. Cataracts were observed in toxicology studies of  
186 eltrombopag in rodents [*see Nonclinical Toxicology (13.2)*]. Perform a baseline ocular  
187 examination prior to administration of PROMACTA and, during therapy with PROMACTA,  
188 regularly monitor patients for signs and symptoms of cataracts.

## 189 **6 ADVERSE REACTIONS**

### 190 **6.1 Clinical Trials Experience**

191 In clinical studies, hemorrhage was the most common serious adverse reaction and most  
192 hemorrhagic reactions followed discontinuation of PROMACTA. Other serious adverse  
193 reactions included liver test abnormalities and thrombotic/thromboembolic complications [*see*  
194 *Warnings and Precautions (5.1, 5.3)*].

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

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

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

205

206 **Table 2. Adverse Reactions ( $\geq 3\%$ ) from Three Placebo-Controlled Studies**

<b>Preferred Term</b>	<b>PROMACTA 50mg n = 241 (%)</b>	<b>Placebo n = 128 (%)</b>
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

207

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

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

215

216 **Table 3. Treatment-Related Adverse Reactions ( $\geq 3\%$ ) from Extension Study**

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

217

218 In a placebo-controlled trial of eltrombopag in non-ITP thrombocytopenic patients with  
219 chronic liver disease (CLD), six eltrombopag-treated patients and one patient in the placebo  
220 group developed portal vein thromboses [see Warnings and Precautions (5.3)].

## 221 **7 DRUG INTERACTIONS**

### 222 **7.1 Cytochrome P450**

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

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

### 237 **7.2 Transporters**

238 *In vitro* studies demonstrate that eltrombopag is an inhibitor of the organic anion  
239 transporting polypeptide OATP1B1 and breast cancer resistance protein (BCRP) and can  
240 increase the systemic exposure of other drugs that are substrates of these transporters (e.g.,  
241 benzylpenicillin, atorvastatin, fluvastatin, pravastatin, rosuvastatin, methotrexate, nateglinide,  
242 repaglinide, rifampin, doxorubicin). Administration of 75 mg of PROMACTA once daily for  
243 5 days with a single 10 mg dose of the OATP1B1 and BCRP substrate, rosuvastatin, to 39  
244 healthy adult subjects increased plasma rosuvastatin AUC<sub>0-∞</sub> by 55% and C<sub>max</sub> by 103%.

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

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

255 **7.3 UDP-glucuronosyltransferases (UGTs)**

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

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

269 **7.4 Polyvalent Cations (Chelation)**

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

279 **8 USE IN SPECIFIC POPULATIONS**

280 **8.1 Pregnancy**

281 Pregnancy Category C

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

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

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

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

298 Pregnant rabbits were treated with oral eltrombopag doses of 30, 80, or 150 mg/kg/day  
299 (0.04, 0.3, and 0.5 times the human clinical exposure based on AUC). No evidence of  
300 fetotoxicity, embryoletality, or teratogenicity was observed.

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

### 306 **8.3 Nursing Mothers**

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

### 311 **8.4 Pediatric Use**

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

### 313 **8.5 Geriatric Use**

314 Of the 106 patients in 2 randomized clinical studies of PROMACTA 50 mg dose, 22%  
315 were 65 years of age and older, and 9% were 75 years of age and older. No overall differences in  
316 safety or efficacy have been observed between older and younger patients in the placebo-  
317 controlled studies, but greater sensitivity of some older individuals cannot be ruled out. In  
318 general, dose adjustment for an elderly patient should be cautious, reflecting the greater  
319 frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other  
320 drug therapy.

### 321 **8.6 Hepatic Impairment**

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

330 Similar results were seen in a population pharmacokinetic (PK) analysis in  
331 thrombocytopenic patients with chronic liver disease following repeat doses of eltrombopag.  
332 However, compared to healthy volunteers, the population PK analysis demonstrated that mild  
333 hepatic impairment resulted in an 87% to 110% higher plasma eltrombopag  $AUC_{(0-\tau)}$  and patients

334 with moderate hepatic impairment had approximately 141% to 240% higher plasma eltrombopag  
335 AUC<sub>(0-τ)</sub> values. The half-life of PROMACTA was prolonged 3-fold in patients with mild  
336 hepatic impairment and 4-fold in patients with moderate hepatic impairment. This clinical study  
337 did not evaluate protein binding effects.

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

## 341 **8.7 Renal Impairment**

342 The disposition of a single 50 mg dose of PROMACTA in patients with mild, moderate,  
343 and severe renal impairment was compared to subjects with normal renal function. Average total  
344 plasma eltrombopag AUC<sub>0-∞</sub> was 32% to 36% lower in subjects with mild to moderate renal  
345 impairment and 60% lower in subjects with severe renal impairment compared with healthy  
346 subjects. The effect of renal impairment on unbound (active) eltrombopag exposure has not been  
347 assessed.

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

## 351 **10 OVERDOSAGE**

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

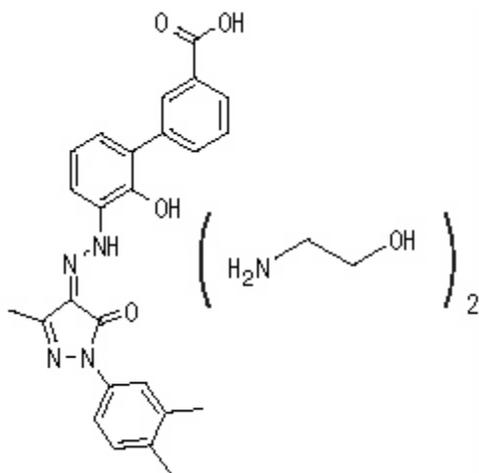
354 In one report, a subject who ingested 5,000 mg of PROMACTA had a platelet count  
355 increase to a maximum of 929 x 10<sup>9</sup>/L at 13 days following the ingestion. The patient also  
356 experienced rash, bradycardia, ALT/AST elevations, and fatigue. The patient was treated with  
357 gastric lavage, oral lactulose, intravenous fluids, omeprazole, atropine, furosemide, calcium,  
358 dexamethasone, and plasmapheresis; however, the abnormal platelet count and liver test  
359 abnormalities persisted for 3 weeks. After 2 months follow-up, all events had resolved without  
360 sequelae.

361 In case of an overdose, consider oral administration of a metal cation-containing  
362 preparation, such as calcium, aluminum, or magnesium preparations to chelate eltrombopag and  
363 thus limit absorption. Closely monitor platelet counts. Reinitiate treatment with PROMACTA in  
364 accordance with dosing and administration recommendations [*see Dosage and Administration*  
365 *(2.2)*].

## 366 **11 DESCRIPTION**

367 PROMACTA (eltrombopag) Tablets contain eltrombopag olamine, a small molecule  
368 thrombopoietin (TPO) receptor agonist for oral administration. Eltrombopag interacts with the  
369 transmembrane domain of the TPO receptor (also known as cMpl) leading to increased platelet  
370 production. Each tablet contains eltrombopag olamine in the amount equivalent to 12.5 mg,  
371 25 mg, 50 mg, or 75 mg of eltrombopag free acid.

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



378  
379           Eltrombopag olamine is practically insoluble in aqueous buffer across a pH range of 1 to  
380 7.4, and is sparingly soluble in water.

381           The inactive ingredients of PROMACTA are: **Tablet Core:** magnesium stearate,  
382 mannitol, microcrystalline cellulose, povidone, and sodium starch glycolate. **Coating:**  
383 hypromellose, polyethylene glycol 400, titanium dioxide, polysorbate 80 (12.5 mg tablet), FD&C  
384 Yellow No. 6 aluminum lake (25 mg tablet), FD&C Blue No. 2 aluminum lake (50 mg tablet), or  
385 Iron Oxide Red and Iron Oxide Black (75 mg tablet).

## 386 **12 CLINICAL PHARMACOLOGY**

### 387 **12.1 Mechanism of Action**

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

### 391 **12.3 Pharmacokinetics**

392           A population pharmacokinetic model analysis suggests that the pharmacokinetic profile  
393 for eltrombopag following oral administration is best described by a 2-compartment model.  
394 Based on this model, the estimated exposures of eltrombopag after administration to patients  
395 with ITP are shown in Table 4.

396

397 **Table 4. Geometric Mean (95% Confidence Intervals) of Steady-State Plasma Eltrombopag**  
 398 **Pharmacokinetic Parameters in Adults With Chronic Immune (Idiopathic)**  
 399 **Thrombocytopenia**

<b>Regimen of PROMACTA</b>	<b>AUC<sub>(0-τ)</sub> (mcg.hr/mL)</b>	<b>C<sub>max</sub> (mcg/mL)</b>
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)

400  
 401 **Absorption:** Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours  
 402 after oral administration. Based on urinary excretion and biotransformation products eliminated  
 403 in feces, the oral absorption of drug-related material following administration of a single 75 mg  
 404 solution dose was estimated to be at least 52%.

405 An open-label, randomized, crossover study was conducted to assess the effect of food on  
 406 the bioavailability of eltrombopag. A standard high-fat breakfast significantly decreased plasma  
 407 eltrombopag AUC<sub>0-∞</sub> by approximately 59% and C<sub>max</sub> by 65% and delayed t<sub>max</sub> by 1 hour. The  
 408 calcium content of this meal may have also contributed to this decrease in exposure.

409 **Distribution:** The concentration of eltrombopag in blood cells is approximately 50% to  
 410 79% of plasma concentrations based on a radiolabel study. *In vitro* studies suggest that  
 411 eltrombopag is highly bound to human plasma proteins (>99%). Eltrombopag is a substrate of  
 412 BCRP, but is not a substrate for P-glycoprotein (P-gp) or OATP1B1.

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

418 **Elimination:** The predominant route of eltrombopag excretion is via feces (59%), and  
 419 31% of the dose is found in the urine. Unchanged eltrombopag in feces accounts for  
 420 approximately 20% of the dose; unchanged eltrombopag is not detectable in urine. The plasma  
 421 elimination half-life of eltrombopag is approximately 21 to 32 hours in healthy subjects and 26  
 422 to 35 hours in ITP patients.

423 **Race:** The influence of East Asian ethnicity (i.e., Japanese, Chinese, Taiwanese, and  
 424 Korean) on the pharmacokinetics of eltrombopag was evaluated using a population  
 425 pharmacokinetic approach in 111 healthy adults (31 East Asians) and 88 patients with ITP (18  
 426 East Asians). After adjusting for body weight differences, East Asians had approximately 50%  
 427 higher plasma eltrombopag AUC<sub>(0-τ)</sub> values as compared to non-East Asian patients who were  
 428 predominantly Caucasian. In a separate population PK analysis of PROMACTA in 28 healthy  
 429 adults (non-East Asians) and 79 patients with chronic liver disease (45 East Asians), East Asian  
 430 patients had approximately 110% higher plasma eltrombopag AUC<sub>(0-τ)</sub> values as compared to

431 non-East Asian patients, after adjusting for body weight differences. A reduction in the initial  
432 dose of PROMACTA is recommended for patients of East Asian ancestry and East Asian  
433 patients with hepatic impairment (Child-Pugh Class A, B, C) [see Dosage and Administration  
434 (2.1)].

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

439 **Gender:** The influence of gender on the pharmacokinetics of eltrombopag was evaluated  
440 using a population pharmacokinetic approach in 111 healthy adults (14 females) and 88 patients  
441 with ITP (57 females). After adjustment for body weight differences, females had approximately  
442 23% higher plasma eltrombopag AUC<sub>(0-τ)</sub> values than males.

#### 443 **12.6 QT/QTc Prolongation**

444 There is no indication of a QT/QTc prolonging effect of PROMACTA at doses up to  
445 150 mg daily for 5 days. The effects of PROMACTA at doses up to 150 mg daily for 5 days  
446 (supratherapeutic doses) on the QT/QTc interval was evaluated in a double-blind, randomized,  
447 placebo- and positive-controlled (moxifloxacin 400 mg, single oral dose) crossover trial in  
448 healthy adult subjects. Assay sensitivity was confirmed by significant QTc prolongation by  
449 moxifloxacin.

### 450 **13 NONCLINICAL TOXICOLOGY**

#### 451 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

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

#### 464 **13.2 Animal Pharmacology/Toxicology**

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

467 Treatment-related cataracts were detected in rodents in a dose- and time-dependent  
468 manner. At ≥6 times the human clinical exposure based on AUC, cataracts were observed in  
469 mice after 6 weeks and in rats after 28 weeks of dosing. At ≥4 times the human clinical exposure

470 based on AUC, cataracts were observed in mice after 13 weeks and in rats after 39 weeks of  
471 dosing. The clinical relevance of these findings is unknown [see Warnings and Precautions  
472 (5.6)].

473 Renal tubular toxicity was observed in studies up to 14 days in duration in mice and rats  
474 at exposures that were generally associated with morbidity and mortality. Tubular toxicity was  
475 also observed in a 2-year oral carcinogenicity study in mice at doses of 25, 75, and  
476 150 mg/kg/day. The exposure at the lowest dose was 1.2 times the human clinical exposure  
477 based on AUC. No similar effects were observed in mice after 13 weeks at exposures greater  
478 than those associated with renal changes in the 2-year study, suggesting that this effect is both  
479 dose- and time-dependent.

## 480 **14 CLINICAL STUDIES**

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

### 484 **14.1 Studies 1 and 2**

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

491 The median age of the patients was 50 years and 60% were female. Approximately 70%  
492 of the patients had received at least 2 prior ITP therapies (predominantly corticosteroids,  
493 immunoglobulins, rituximab, cytotoxic therapies, danazol, and azathioprine) and 40% of the  
494 patients had undergone splenectomy. The median baseline platelet counts (approximately  $18 \times$   
495  $10^9/L$ ) were similar among all treatment groups.

496 Study 1 randomized 114 patients (2:1) to PROMACTA 50 mg or placebo. Study 2  
497 randomized 117 patients (1:1:1:1) among placebo or 1 of 3 dose regimens of PROMACTA,  
498 30 mg, 50 mg, or 75 mg each administered daily.

499 Table 5 shows for each study the primary efficacy outcomes for the placebo groups and  
500 the patient groups who received the 50 mg daily regimen of PROMACTA.

501

502 **Table 5. Studies 1 and 2 Platelet Count Response ( $\geq 50 \times 10^9/L$ ) Rates**

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

503 <sup>a</sup> P value  $<0.001$  for PROMACTA versus placebo.

504

505 The platelet count response to PROMACTA was similar among patients who had or had  
506 not undergone splenectomy. In general, increases in platelet counts were detected 1 week  
507 following initiation of PROMACTA and the maximum response was observed after 2 weeks of  
508 therapy. In the placebo and 50 mg dose groups of PROMACTA, the study drug was discontinued  
509 due to an increase in platelet counts to  $>200 \times 10^9/L$  in 3% and 27% of the patients, respectively.  
510 The median duration of treatment with the 50 mg dose of PROMACTA was 42 days in Study 1  
511 and 43 days in Study 2.

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

### 516 **14.2 Study 3**

517 In this study, 197 patients were randomized (2:1) to receive either PROMACTA 50 mg  
518 once daily (n = 135) or placebo (n = 62) for 6 months, during which time the dose of  
519 PROMACTA could be adjusted based on individual platelet counts. Patients were allowed to  
520 taper or discontinue concomitant ITP medications after being treated with PROMACTA for  
521 6 weeks. Patients were permitted to receive rescue treatments at any time during the study as  
522 clinically indicated. The primary endpoint was the odds of achieving a platelet count  $\geq 50 \times 10^9/L$   
523 and  $\leq 400 \times 10^9/L$  for patients receiving PROMACTA relative to placebo and was based on  
524 patient response profiles throughout the 6-month treatment period.

525 The median age of the patients treated with PROMACTA and placebo was 47 years and  
526 52.5 years, respectively. Approximately half of the patients treated with PROMACTA and  
527 placebo (47% and 50%, respectively) were receiving concomitant ITP medication  
528 (predominantly corticosteroids) at randomization and had baseline platelet counts  $\leq 15 \times 10^9/L$   
529 (50% and 48%, respectively). A similar percentage of patients treated with PROMACTA and  
530 placebo (37% and 34%, respectively) had a prior splenectomy.

531 In 134 patients who completed 26 weeks of treatment, a sustained platelet response  
532 (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  
533 treatment period in the absence of rescue medication at any time) was achieved by 60% of  
534 patients treated with PROMACTA, compared to 10% of patients treated with placebo  
535 (splenectomized patients: PROMACTA 51%, placebo 8%; non-splenectomized patients:  
536 PROMACTA 66%, placebo 11%). The proportion of responders in the PROMACTA treatment  
537 group was between 37% and 56% compared to 7% and 19% in the placebo treatment group for  
538 all on-therapy visits. Patients treated with PROMACTA were significantly more likely to  
539 achieve a platelet count between  $50 \times 10^9/L$  and  $400 \times 10^9/L$  during the entire 6-month treatment  
540 period compared to those patients treated with placebo.

541 Outcomes of treatment are presented in Table 6 for all patients enrolled in the study.  
542

543 **Table 6. Outcomes of Treatment from the Study 3**

<b>Outcome</b>	<b>PROMACTA N = 135</b>	<b>Placebo N = 62</b>
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)

544

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

548 **14.3 Extension Study**

549 Patients who completed any prior clinical study with PROMACTA were enrolled in an  
550 open-label, single-arm study in which attempts were made to decrease the dose or eliminate the  
551 need for any concomitant ITP medications. PROMACTA was administered to 299 patients; 249  
552 completed 6 months, 210 patients completed 12 months, and 138 patients completed 24 months  
553 of therapy. The median baseline platelet count was  $19 \times 10^9/L$  prior to administration of  
554 PROMACTA.

555 **16 HOW SUPPLIED/STORAGE AND HANDLING**

556 The 12.5 mg tablets are round, biconvex, white, film-coated tablets debossed with GS  
557 MZ1 and 12.5 on one side and are available in bottles of 30: NDC 0007-4643-13.

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

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

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

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

566 **17 PATIENT COUNSELING INFORMATION**

567 See FDA-approved patient labeling (Medication Guide).

568 **17.1 Information for Patients**

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

- 571 • Therapy with PROMACTA is administered to achieve and maintain a platelet count  $\geq 50 \times$   
572  $10^9/L$  as necessary to reduce the risk for bleeding; PROMACTA is not used to normalize  
573 platelet counts.
- 574 • Therapy with PROMACTA may be associated with hepatobiliary laboratory abnormalities.  
575 Monitor serum liver tests (ALT, AST, and bilirubin) prior to initiation of PROMACTA,

- 576 every 2 weeks during the dose adjustment phase, and monthly following establishment of a  
577 stable dose. If bilirubin is elevated, perform fractionation.
- 578 • Inform patients that they should report any of the following signs and symptoms of liver  
579 problems to their healthcare provider right away.
    - 580 • yellowing of the skin or the whites of the eyes (jaundice)
    - 581 • unusual darkening of the urine
    - 582 • unusual tiredness
    - 583 • right upper stomach area pain
  - 584 • Following discontinuation of PROMACTA, thrombocytopenia and risk of bleeding may  
585 reoccur, particularly if PROMACTA is discontinued while the patient is on anticoagulants or  
586 antiplatelet agents.
  - 587 • Therapy with PROMACTA may increase the risk of reticulin fiber formation within the bone  
588 marrow. Detection of peripheral blood cell abnormalities may necessitate a bone marrow  
589 examination.
  - 590 • Too much PROMACTA may result in excessive platelet counts and a risk for  
591 thrombotic/thromboembolic complications.
  - 592 • PROMACTA stimulates certain bone marrow cells to make platelets. Drugs acting in this  
593 manner may increase the risk for progression of underlying MDS or other hematological  
594 conditions. Platelet counts and CBCs must be performed regularly while taking  
595 PROMACTA.
  - 596 • Patients must be closely monitored with weekly platelet counts and CBCs for at least  
597 4 weeks following discontinuation of PROMACTA.
  - 598 • Even during therapy with PROMACTA, patients should continue to avoid situations or  
599 medications that may increase the risk for bleeding.
  - 600 • Patients must be advised to keep at least a 4-hour interval between PROMACTA and foods,  
601 mineral supplements, and antacids which contain polyvalent cations such as iron, calcium,  
602 aluminum, magnesium, selenium, and zinc.

603  
604 PROMACTA is a registered trademark of GlaxoSmithKline.  
605



606  
607 GlaxoSmithKline  
608 Research Triangle Park, NC 27709  
609  
610 ©YEAR, GlaxoSmithKline. All rights reserved.  
611  
612 Month YEAR  
613 PRM:XPI



41 or stop PROMACTA if your platelet counts get too high. Tell your healthcare  
42 provider right away if you have signs and symptoms of a blood clot in the leg,  
43 such as swelling, pain, or tenderness in your leg.

44 People with chronic liver disease may be at risk for a type of blood clot in the  
45 stomach area. Stomach area pain may be a symptom of this type of blood clot.

- 46 • **Worsening of blood cancers.** PROMACTA is not for use in people with blood  
47 cancer or a precancerous condition called myelodysplastic syndrome (MDS). If  
48 you have one of these conditions, PROMACTA may worsen your cancer or  
49 condition and may cause you to die sooner.
- 50 • **New or worsened cataracts (a clouding of the lens in the eye).** New  
51 or worsened cataracts have happened in people taking PROMACTA. Your  
52 healthcare provider will check your eyes before and during your treatment with  
53 PROMACTA. Tell your healthcare provider about any changes in your eyesight  
54 while taking PROMACTA.

55

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

59

60 **See “What are the possible side effects of PROMACTA?” for other side**  
61 **effects of PROMACTA.**

62

### 63 **What is PROMACTA?**

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

68

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

72

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

75

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

78

### 79 **What should I tell my healthcare provider before taking PROMACTA?**

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

- 81 • have liver or kidney problems
- 82 • have or had a blood clot
- 83 • have a history of cataracts
- 84 • have had surgery to remove your spleen (splenectomy)
- 85 • have a bone marrow problem, including a blood cancer or Myelodysplastic
- 86     Syndrome (MDS)
- 87 • have bleeding problems
- 88 • are Asian and you are of Chinese, Japanese, Taiwanese, or Korean ancestry, you
- 89     may need a lower dose of PROMACTA.
- 90 • have any other medical conditions
- 91 • are pregnant, think you may be pregnant, or plan to get pregnant. It is not
- 92     known if PROMACTA will harm an unborn baby.
- 93     ***Pregnancy Registry:*** There is a registry for women who become pregnant
- 94     during treatment with PROMACTA. If you become pregnant, consider this
- 95     registry. The purpose of the registry is to collect safety information about the
- 96     health of you and your baby. Contact the registry as soon as you become aware
- 97     of the pregnancy, or ask your healthcare provider to contact the registry for
- 98     you. You and your healthcare provider can get information and enroll in the
- 99     registry by calling 1-888-825-5249.
- 100 • are breast-feeding or plan to breast-feed. It is not known if PROMACTA passes
- 101     into your breast milk. You and your healthcare provider should decide whether
- 102     you will take PROMACTA or breast-feed. You should not do both.

103

104 **Tell your healthcare provider about all the medicines you take**, including

105 prescription and non-prescription medicines, vitamins, and herbal products.

106 PROMACTA may affect the way certain medicines work. Certain other medicines

107 may affect the way PROMACTA works.

- 108
- 109 Especially tell your healthcare provider if you take:
- 110 • certain medicines used to treat high cholesterol, called “statins”.
  - 111 • a blood thinner medicine.

112

113 Certain medicines may keep PROMACTA from working correctly. Take PROMACTA

114 either 4 hours before or 4 hours after taking these products:

- 115 • antacids used to treat stomach ulcers or heartburn.
- 116 • multivitamins or products that contain iron, calcium, aluminum, magnesium,
- 117     selenium, and zinc which may be found in mineral supplements.

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

119 above.

120

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

123

#### 124 **How should I take PROMACTA?**

- 125 • Take PROMACTA exactly as your healthcare provider tells you. Do not stop using  
126 PROMACTA without talking with your healthcare provider first. Do not change  
127 your dose or schedule for taking PROMACTA unless your healthcare provider  
128 tells you to change it.
- 129 • Take PROMACTA on an empty stomach, either 1 hour before or 2 hours after  
130 eating food.
- 131 • Take PROMACTA at least 4 hours before or 4 hours after eating dairy products  
132 and calcium fortified juices.
- 133 • If you miss a dose of PROMACTA, wait and take your next scheduled dose. Do  
134 not take more than one dose of PROMACTA in one day.
- 135 • If you take too much PROMACTA, you may have a higher chance of serious side  
136 effects. Call your healthcare provider right away.
- 137 • Your healthcare provider will check your platelet count every week and change  
138 your dose of PROMACTA as needed. This will happen every week until your  
139 healthcare provider decides that your dose of PROMACTA can stay the same.  
140 After that, you will need to have blood tests every month. When you stop taking  
141 PROMACTA, you will need to have blood tests for at least 4 weeks to check if  
142 your platelet count drops too low.
- 143 • Tell your healthcare provider about any bruising or bleeding that happens while  
144 you take and after you stop taking PROMACTA.

145

#### 146 **What should I avoid while taking PROMACTA?**

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

148

#### 149 **What are the possible side effects of PROMACTA?**

150 PROMACTA may cause serious side effects.

151

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

154

155 The most common side effects of PROMACTA are:

- 156 • nausea
- 157 • diarrhea
- 158 • upper respiratory tract infection; symptoms may include runny nose, stuffy  
159 nose, and sneezing
- 160 • vomiting

- 161 • muscle aches
- 162 • urinary tract infections; symptoms may include frequent or urgent need to
- 163 urinate, low fever in some people, pain or burning with urination
- 164 • pain or swelling (inflammation) in your throat or mouth (oropharyngeal pain and
- 165 pharyngitis)
- 166 • abnormal liver function tests
- 167 • abnormal skin sensations such as tingling, itching, or burning
- 168 • back pain
- 169 • 'flu' symptoms (influenza); symptoms may include fever, headache, tiredness,
- 170 cough, sore throat, and body aches
- 171 • rash
- 172

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

176  
177 Call your doctor for medical advice about side effects. You may report side effects  
178 to FDA at 1-800-FDA-1088.

179  
180 **How should I store PROMACTA Tablets?**

- 181 • Store at room temperature between 59°F to 86°F (15°C to 30°C).
- 182 • **Keep PROMACTA and all medicines out of the reach of children.**
- 183

184 **General information about the safe and effective use of PROMACTA**

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

189  
190 This Medication Guide summarizes the most important information about  
191 PROMACTA. If you would like more information, talk with your healthcare provider.  
192 You can ask your healthcare provider or pharmacist for information about  
193 PROMACTA that is written for healthcare professionals.

194  
195 For more information, go to [www.PROMACTA.com](http://www.PROMACTA.com) or call toll-free 1-888-825-5249.

196  
197 **What are the ingredients in PROMACTA?**

198 Active ingredient: eltrombopag olamine.

199 Inactive ingredients:

- 200 • Tablet Core: Magnesium stearate, mannitol, microcrystalline cellulose, povidone,  
201 and sodium starch glycolate.
- 202 • Coating: Hypromellose, polyethylene glycol 400, titanium dioxide, polysorbate  
203 80 (12.5 mg tablet), and FD&C Yellow No. 6 aluminum lake (25 mg tablet),  
204 FD&C Blue No. 2 aluminum lake (50 mg tablet), or Iron Oxide Red and Iron  
205 Oxide Black (75 mg tablet).

206

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

209

210 PROMACTA is a registered trademark of GlaxoSmithKline.

211



212

213 GlaxoSmithKline

214 Research Triangle Park, NC 27709

215

216 ©YEAR, GlaxoSmithKline. All rights reserved.

217

218 Revised: December 2011

219 PRM: XMG