

**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  $\geq 3X$  upper limit of normal (ULN) in patients with normal liver function or  $\geq 3X$  baseline in patients with pre-treatment elevations in transaminases 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	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  $\geq 50 \times 10^9/L$ . 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  $\geq 10$  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 ( $\geq 3\%$  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 ( $\geq 10\%$  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](http://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

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## 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  $\geq 3X$  the upper limit of normal (ULN) in patients with normal liver function or  $\geq 3X$  baseline in patients with pre-treatment elevations in transaminases 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.

## 1 INDICATIONS AND USAGE

### 1.1 Treatment of Thrombocytopenia in Patients with Chronic ITP

PROMACTA<sup>®</sup> 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.

37 **2 DOSAGE AND ADMINISTRATION**

38 **2.1 Chronic Immune (Idiopathic) Thrombocytopenia**

39 Use the lowest dose of PROMACTA to achieve and maintain a platelet count greater than  
40 or equal to  $50 \times 10^9/L$  as necessary to reduce the risk for bleeding. Dose adjustments are based  
41 upon the platelet count response. Do not use PROMACTA to normalize platelet counts [*see*  
42 *Warnings and Precautions (5.4)*]. In clinical studies, platelet counts generally increased within 1  
43 to 2 weeks after starting PROMACTA and decreased within 1 to 2 weeks after discontinuing  
44 PROMACTA [*see Clinical Studies (14)*].

45 **Initial Dose Regimen:** Initiate PROMACTA at a dose of 50 mg once daily, except in  
46 patients who are of East Asian ancestry (such as Chinese, Japanese, Taiwanese, or Korean) or  
47 who have mild to severe hepatic impairment (Child-Pugh Class A, B, C).

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

50 For ITP patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A,  
51 B, C), initiate PROMACTA at a reduced dose of 25 mg once daily [*see Use in Specific*  
52 *Populations (8.6) and Clinical Pharmacology (12.3)*].

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

56 **Monitoring and Dose Adjustment:** After initiating PROMACTA, adjust the dose to  
57 achieve and maintain a platelet count greater than or equal to  $50 \times 10^9/L$  as necessary to reduce  
58 the risk for bleeding. Do not exceed a dose of 75 mg daily. Monitor clinical hematology and liver  
59 tests regularly throughout therapy with PROMACTA and modify the dosage regimen of  
60 PROMACTA based on platelet counts as outlined in Table 1. During therapy with PROMACTA,  
61 assess CBCs with differentials (including platelet counts) weekly until a stable platelet count has  
62 been achieved. Obtain CBCs with differentials (including platelet counts) monthly thereafter.

63

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

Platelet Count Result	Dose Adjustment or Response
<50 x 10 <sup>9</sup> /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.
≥200 x 10 <sup>9</sup> /L to ≤400 x 10 <sup>9</sup> /L at any time	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
>400 x 10 <sup>9</sup> /L	Stop PROMACTA; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is <150 x 10 <sup>9</sup> /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 x 10 <sup>9</sup> /L after 2 weeks of therapy at lowest dose of PROMACTA	Discontinue PROMACTA.

66

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

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

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

## 77 **2.2 Chronic Hepatitis C-Associated Thrombocytopenia**

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

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

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

87 During antiviral therapy, adjust the dose of PROMACTA to avoid dose reductions of  
88 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 x 10 <sup>9</sup> /L following at least 2 weeks of PROMACTA	Increase daily dose by 25 mg to a maximum of 100 mg/day.
≥200 x 10 <sup>9</sup> /L to ≤400 x 10 <sup>9</sup> /L at any time	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
>400 x 10 <sup>9</sup> /L	Stop PROMACTA; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is <150 x 10 <sup>9</sup> /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 x 10 <sup>9</sup> /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)*].

112 **3 DOSAGE FORMS AND STRENGTHS**

- 113 • 12.5 mg tablets — round, biconvex, white, film-coated tablets debossed with GS MZ1 and  
114 12.5 on one side. Each tablet, for oral administration, contains eltrombopag olamine,  
115 equivalent to 12.5 mg of eltrombopag free acid.
- 116 • 25 mg tablets — round, biconvex, orange, film-coated tablets debossed with GS NX3 and 25  
117 on one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to  
118 25 mg of eltrombopag free acid.
- 119 • 50 mg tablets — round, biconvex, blue, film-coated tablets debossed with GS UFU and 50 on  
120 one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to 50  
121 mg of eltrombopag free acid.
- 122 • 75 mg tablets — round, biconvex, pink, film-coated tablets debossed with GS FFS and 75 on  
123 one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to  
124 75 mg of eltrombopag free acid.
- 125 • 100 mg tablets — round, biconvex, green, film-coated tablets debossed with GS 1L5 and  
126 100 on one side. Each tablet, for oral administration, contains eltrombopag olamine,  
127 equivalent to 100 mg of eltrombopag free acid.

128 **4 CONTRAINDICATIONS**

129 None.

130 **5 WARNINGS AND PRECAUTIONS**

131 **5.1 Hepatotoxicity**

132 PROMACTA may cause hepatotoxicity. In the controlled clinical studies in chronic ITP,  
133 one patient experienced Grade 4 (NCI Common Terminology Criteria for Adverse Events [NCI  
134 CTCAE] toxicity scale) elevations in serum liver test values during therapy with PROMACTA,  
135 worsening of underlying cardiopulmonary disease, and death. One patient in the placebo group  
136 experienced a Grade 4 liver test abnormality. Overall, serum liver test abnormalities  
137 (predominantly Grade 2 or less in severity) were reported in 11% and 7% of the PROMACTA  
138 and placebo groups, respectively. In the 3 controlled chronic ITP studies, four patients (1%)  
139 treated with PROMACTA and three patients in the placebo group (2%) discontinued treatment  
140 due to hepatobiliary laboratory abnormalities. Seven of the patients treated with PROMACTA in  
141 the controlled studies with hepatobiliary laboratory abnormalities were re-exposed to  
142 PROMACTA in the extension trial. Six of these patients again experienced liver test  
143 abnormalities (predominantly Grade 1) resulting in discontinuation of PROMACTA in one  
144 patient. In the extension chronic ITP trial, one additional patient had PROMACTA discontinued  
145 due to liver test abnormalities ( $\leq$ Grade 3).

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

151 Measure serum ALT, AST, and bilirubin prior to initiation of PROMACTA, every  
152 2 weeks during the dose adjustment phase, and monthly following establishment of a stable dose.  
153 If bilirubin is elevated, perform fractionation. Evaluate abnormal serum liver tests with repeat  
154 testing within 3 to 5 days. If the abnormalities are confirmed, monitor serum liver tests weekly  
155 until the abnormality(ies) resolve, stabilize, or return to baseline levels. Discontinue  
156 PROMACTA if ALT levels increase to  $\geq 3X$  ULN in patients with normal liver function or  $\geq 3X$   
157 baseline in patients with pre-treatment elevations in transaminases and are:

- 158 • progressive, or
- 159 • persistent for  $\geq 4$  weeks, or
- 160 • accompanied by increased direct bilirubin, or
- 161 • accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation.

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

## 167 **5.2 Hepatic Decompensation in Patients with Chronic Hepatitis C**

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

## 177 **5.3 Bone Marrow Reticulin Formation and Risk for Bone Marrow Fibrosis**

178 PROMACTA may increase the risk for development or progression of reticulin fiber  
179 deposition within the bone marrow. In the extension trial in chronic ITP, 151 patients have had  
180 bone marrow biopsies evaluated for increased reticulin and collagen fiber deposition. Bone  
181 marrow biopsies taken after 1 year of therapy showed predominantly myelofibrosis (MF) Grade  
182 1 or less in 140/151 (93%) of patients. There were 11/151 (7%) of patients with MF Grade 2.  
183 Four patients had collagen deposition reported. One patient with a pre-existing MF Grade 1  
184 developed a MF Grade 2 and subsequently discontinued treatment with PROMACTA. Clinical  
185 studies have not demonstrated clinical consequences to date. If new or worsening blood  
186 morphological abnormalities or cytopenias occur, consider a bone marrow biopsy including  
187 staining for fibrosis.

## 188 **5.4 Thrombotic/Thromboembolic Complications**

189 In 2 controlled clinical trials in patients with chronic hepatitis C and thrombocytopenia,  
190 3% (31/955) treated with PROMACTA experienced a thrombotic event compared to 1% (5/484)

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

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

196 Consider the potential for an increased risk of thromboembolism when administering  
197 PROMACTA to patients with known risk factors for thromboembolism (e.g., Factor V Leiden,  
198 ATIII deficiency, antiphospholipid syndrome, chronic liver disease). To minimize the risk for  
199 thrombotic/thromboembolic complications, do not use PROMACTA in an attempt to normalize  
200 platelet counts. Follow the dose adjustment guidelines to achieve and maintain target platelet  
201 counts [*see Dosage and Administration (2.1, 2.2)*].

202 In a controlled trial in non-ITP thrombocytopenic patients with chronic liver disease  
203 undergoing elective invasive procedures (N = 292), the risk of thrombotic events was increased  
204 in patients treated with 75 mg PROMACTA once daily. Seven thrombotic complications (six  
205 patients) were reported in the group that received PROMACTA and three thrombotic  
206 complications were reported in the placebo group (two patients). All of the thrombotic  
207 complications reported in the group that received PROMACTA were portal vein thrombosis  
208 (PVT). Symptoms of PVT included abdominal pain, nausea, vomiting, and diarrhea. Five of the  
209 six patients in the group that received PROMACTA experienced a thrombotic complication  
210 within 30 days of completing treatment with PROMACTA and at a platelet count above  $200 \times 10^9/L$ .  
211 The risk of portal venous thrombosis was increased in thrombocytopenic patients with  
212 chronic liver disease treated with 75 mg PROMACTA once daily for 2 weeks in preparation for  
213 invasive procedures.

## 214 **5.5 Laboratory Monitoring**

215 **Complete Blood Counts (CBCs):** Obtain CBCs with differentials (including platelet  
216 counts) weekly during the dose adjustment phase of therapy with PROMACTA and then  
217 monthly following establishment of a stable dose of PROMACTA. Obtain CBCs with  
218 differentials (including platelet counts) weekly for at least 4 weeks following discontinuation of  
219 PROMACTA. [*See Dosage and Administration (2.1, 2.2) and Warnings and Precautions (5.3).*]

220 **Liver Tests:** Monitor serum liver tests (ALT, AST, and bilirubin) prior to initiation of  
221 PROMACTA, every 2 weeks during the dose adjustment phase, and monthly following  
222 establishment of a stable dose. PROMACTA inhibits UGT1A1 and OATP1B1, which may lead  
223 to indirect hyperbilirubinemia. If bilirubin is elevated, perform fractionation. If abnormal levels  
224 are detected, repeat the tests within 3 to 5 days. If the abnormalities are confirmed, monitor  
225 serum liver tests weekly until the abnormality(ies) resolve, stabilize, or return to baseline levels.  
226 Discontinue PROMACTA for the development of important liver test abnormalities [*see*  
227 *Warnings and Precautions (5.1)*].

## 228 **5.6 Cataracts**

229 In the 3 controlled clinical trials in chronic ITP, cataracts developed or worsened in 15  
230 (7%) patients who received 50 mg PROMACTA daily and 8 (7%) placebo-group patients. In the

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

235 Cataracts were observed in toxicology studies of eltrombopag in rodents [see *Nonclinical*  
236 *Toxicology (13.2)*]. Perform a baseline ocular examination prior to administration of  
237 PROMACTA and, during therapy with PROMACTA, regularly monitor patients for signs and  
238 symptoms of cataracts.

## 239 **6 ADVERSE REACTIONS**

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

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

### 249 **6.1 Clinical Trials Experience**

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

253 Chronic Immune (Idiopathic) Thrombocytopenic: In clinical studies, hemorrhage was  
254 the most common serious adverse reaction and most hemorrhagic reactions followed  
255 discontinuation of PROMACTA. Other serious adverse reactions included liver test  
256 abnormalities and thrombotic/thromboembolic complications [see *Warnings and Precautions*  
257 *(5.1, 5.4)*].

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

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

265

266 **Table 3. Adverse Reactions ( $\geq 3\%$ ) from Three Placebo-Controlled Studies in Adults With**  
267 **Chronic Immune (Idiopathic) Thrombocytopenia**

<b>Adverse Reaction</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

268  
269 In the 3 controlled clinical chronic ITP studies, alopecia, musculoskeletal pain, blood  
270 alkaline phosphatase increased, and dry mouth were the adverse reactions reported in 2% of  
271 patients treated with PROMACTA and in no patients who received placebo.

272 Among 299 patients with chronic ITP who received PROMACTA in the single-arm  
273 extension trial, the adverse reactions occurred in a pattern similar to that seen in the placebo-  
274 controlled studies. Table 4 presents the most common treatment-related adverse reactions  
275 (experienced by  $\geq 3\%$  of patients receiving PROMACTA) from the extension trial.  
276

277 **Table 4. Treatment-Related Adverse Reactions ( $\geq 3\%$ ) from Extension Trial in Adults With**  
278 **Chronic Immune (Idiopathic) Thrombocytopenia**

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

279

280 In a placebo-controlled trial of PROMACTA in non-ITP thrombocytopenic patients with  
281 chronic liver disease, six patients in the PROMACTA group and one patient in the placebo group  
282 developed portal vein thromboses [see *Warnings and Precautions (5.3)*].

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

287

288 **Table 5. Adverse Reactions ( $\geq 10\%$  and Greater than Placebo) from Two Placebo-**  
 289 **Controlled Studies in Adults With Chronic Hepatitis C**  
 290

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

291  
 292 In the 2 controlled clinical studies in patients with chronic hepatitis C, hyperbilirubinemia  
 293 was also reported (8% for PROMACTA versus 3% for placebo).

294 **7 DRUG INTERACTIONS**

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

300 **7.1 Polyvalent Cations (Chelation)**

301 Eltrombopag chelates polyvalent cations (such as iron, calcium, aluminum, magnesium,  
 302 selenium, and zinc) in foods, mineral supplements, and antacids. In a clinical trial, administration  
 303 of PROMACTA with a polyvalent cation-containing antacid decreased plasma eltrombopag  
 304 systemic exposure by approximately 70% [see *Clinical Pharmacology (12.3)*].

305 PROMACTA must not be taken within 4 hours of any medications or products  
 306 containing polyvalent cations such as antacids, dairy products, and mineral supplements to avoid

307 significant reduction in PROMACTA absorption due to chelation [*see Dosage and*  
308 *Administration (2)*].

## 309 **7.2 Transporters**

310 Co-administration of PROMACTA with the OATP1B1 and BCRP substrate,  
311 rosuvastatin, to healthy adult subjects increased plasma rosuvastatin AUC<sub>0-∞</sub> by 55% and C<sub>max</sub> by  
312 103% [*see Clinical Pharmacology (12.3)*].

313 Use caution when concomitantly administering PROMACTA and drugs that are  
314 substrates of OATP1B1 [e.g., atorvastatin, bosentan, ezetimibe, fluvastatin, glyburide,  
315 olmesartan, pitavastatin, pravastatin, rosuvastatin, repaglinide, rifampin, simvastatin acid, SN-38  
316 (active metabolite of irinotecan), valsartan] or BCRP (e.g., imatinib, irinotecan, lapatinib,  
317 methotrexate, mitoxantrone, rosuvastatin, sulfasalazine, topotecan). Monitor patients closely for  
318 signs and symptoms of excessive exposure to the drugs that are substrates of OATP1B1 or  
319 BCRP and consider reduction of the dose of these drugs, if appropriate. In clinical trials with  
320 PROMACTA, a dose reduction of rosuvastatin by 50% was recommended.

## 321 **7.3 Lopinavir/ritonavir**

322 In a drug interaction study, co-administration of PROMACTA with lopinavir/ritonavir  
323 (LPV/RTV) decreased plasma eltrombopag exposure by 17% [*see Clinical Pharmacology*  
324 *(12.3)*]. No dose adjustment is recommended when PROMACTA is co-administered with  
325 LPV/RTV. Drug interactions with other HIV protease inhibitors have not been evaluated.

## 326 **7.4 Peginterferon Alfa 2a/b Therapy**

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

# 330 **8 USE IN SPECIFIC POPULATIONS**

## 331 **8.1 Pregnancy**

332 Pregnancy Category C

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

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

341 In an early embryonic development study, female rats received oral eltrombopag at doses  
342 of 10, 20, or 60 mg/kg/day (0.8, 2, and 6 times, respectively, the human clinical exposure based  
343 on AUC in ITP patients at 75 mg/day and 0.3, 1, and 3 times, respectively, the human clinical  
344 exposure based on AUC in chronic hepatitis C patients at 100 mg/day). Increased pre- and post-

345 implantation loss and reduced fetal weight were observed at the highest dose which also caused  
346 maternal toxicity.

347       Eltrombopag was administered orally to pregnant rats at 10, 20, or 60 mg/kg/day (0.8, 2,  
348 and 6 times, respectively, the human clinical exposure based on AUC in ITP patients at 75  
349 mg/day and 0.3, 1, and 3 times, respectively, the human clinical exposure based on AUC in  
350 chronic hepatitis C patients at 100 mg/day). Decreased fetal weights (6% to 7%) and a slight  
351 increase in the presence of cervical ribs were observed at the highest dose which also caused  
352 maternal toxicity. However, no evidence of major structural malformations was observed.

353       Pregnant rabbits were treated with oral eltrombopag doses of 30, 80, or 150 mg/kg/day  
354 (0.04, 0.3, and 0.5 times, respectively, the human clinical exposure based on AUC in ITP  
355 patients at 75 mg/day and 0.02, 0.1, and 0.3 times, respectively, the human clinical exposure  
356 based on AUC in chronic hepatitis C patients at 100 mg/day). No evidence of fetotoxicity,  
357 embryoletality, or teratogenicity was observed.

358       In a pre- and post-natal developmental toxicity study in pregnant rats (F0), no adverse  
359 effects on maternal reproductive function or on the development of the offspring (F1) were  
360 observed at doses up to 20 mg/kg/day (2 times the human clinical exposure based on AUC in  
361 ITP patients at 75 mg/day and similar to the human clinical exposure based on AUC in chronic  
362 hepatitis C patients at 100 mg/day). Eltrombopag was detected in the plasma of offspring (F1).  
363 The plasma concentrations in pups increased with dose following administration of drug to the  
364 F0 dams.

### 365 **8.3 Nursing Mothers**

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

### 370 **8.4 Pediatric Use**

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

### 372 **8.5 Geriatric Use**

373       Of the 106 patients in 2 randomized clinical studies of PROMACTA 50 mg in chronic  
374 ITP, 22% were 65 years of age and over, while 9% were 75 years of age and over. In the 2  
375 randomized clinical trials of PROMACTA in patients with chronic hepatitis C and  
376 thrombocytopenia, 7% were 65 years of age and over, while fewer than 1% were 75 years of age  
377 and over. No overall differences in safety or effectiveness were observed between these patients  
378 and younger patients in the placebo-controlled studies, but greater sensitivity of some older  
379 individuals cannot be ruled out.

### 380 **8.6 Hepatic Impairment**

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

383       A reduction in the initial dose of PROMACTA in patients with chronic ITP is  
384 recommended for patients with hepatic impairment (Child-Pugh Class A, B, C) [*see Dosage and*

385 Administration (2.1) and Warnings and Precautions (5.1)]. No dosage adjustment is necessary  
386 for HCV patients with hepatic impairment [see Clinical Pharmacology (12.3)].

### 387 **8.7 Renal Impairment**

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

### 391 **8.8 Ethnicity**

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

## 398 **10 OVERDOSAGE**

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

401 In one report, a subject who ingested 5,000 mg of PROMACTA had a platelet count  
402 increase to a maximum of  $929 \times 10^9/L$  at 13 days following the ingestion. The patient also  
403 experienced rash, bradycardia, ALT/AST elevations, and fatigue. The patient was treated with  
404 gastric lavage, oral lactulose, intravenous fluids, omeprazole, atropine, furosemide, calcium,  
405 dexamethasone, and plasmapheresis; however, the abnormal platelet count and liver test  
406 abnormalities persisted for 3 weeks. After 2 months follow-up, all events had resolved without  
407 sequelae.

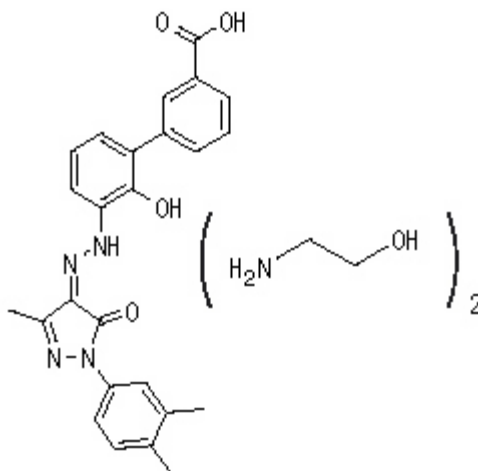
408 In case of an overdose, consider oral administration of a metal cation-containing  
409 preparation, such as calcium, aluminum, or magnesium preparations to chelate eltrombopag and  
410 thus limit absorption. Closely monitor platelet counts. Reinitiate treatment with PROMACTA in  
411 accordance with dosing and administration recommendations [see Dosage and Administration  
412 (2.2)].

## 413 **11 DESCRIPTION**

414 PROMACTA (eltrombopag) Tablets contain eltrombopag olamine, a small molecule  
415 thrombopoietin (TPO) receptor agonist for oral administration. Eltrombopag interacts with the  
416 transmembrane domain of the TPO receptor (also known as cMpl) leading to increased platelet  
417 production. Each tablet contains eltrombopag olamine in the amount equivalent to 12.5 mg,  
418 25 mg, 50 mg, 75 mg, or 100 mg of eltrombopag free acid.

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

423 olamine and 442.5 for eltrombopag free acid. Eltrombopag olamine has the following structural  
424 formula:



425  
426 Eltrombopag olamine is practically insoluble in aqueous buffer across a pH range of 1 to  
427 7.4, and is sparingly soluble in water.

428 The inactive ingredients of PROMACTA are: **Tablet Core:** magnesium stearate,  
429 mannitol, microcrystalline cellulose, povidone, and sodium starch glycolate. **Coating:**  
430 hypromellose, polyethylene glycol 400, titanium dioxide, polysorbate 80 (12.5 mg tablet), FD&C  
431 Yellow No. 6 aluminum lake (25 mg tablet), FD&C Blue No. 2 aluminum lake (50 mg tablet),  
432 Iron Oxide Red and Iron Oxide Black (75 mg tablet), or Iron Oxide Yellow and Iron Oxide  
433 Black (100 mg tablet).

## 434 **12 CLINICAL PHARMACOLOGY**

### 435 **12.1 Mechanism of Action**

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

### 439 **12.3 Pharmacokinetics**

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

444 An open-label, randomized, crossover trial was conducted to assess the effect of food on  
445 the bioavailability of eltrombopag. A standard high-fat breakfast significantly decreased plasma  
446 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  
447 calcium content of this meal may have also contributed to this decrease in exposure.

448 **Distribution:** The concentration of eltrombopag in blood cells is approximately 50% to  
449 79% of plasma concentrations based on a radiolabel study. *In vitro* studies suggest that  
450 eltrombopag is highly bound to human plasma proteins (>99%). Eltrombopag is a substrate of  
451 BCRP, but is not a substrate for P-glycoprotein (P-gp) or OATP1B1.

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

457 **Elimination:** The predominant route of eltrombopag excretion is via feces (59%), and  
458 31% of the dose is found in the urine. Unchanged eltrombopag in feces accounts for  
459 approximately 20% of the dose; unchanged eltrombopag is not detectable in urine. The plasma  
460 elimination half-life of eltrombopag is approximately 21 to 32 hours in healthy subjects and 26  
461 to 35 hours in ITP patients.

462 **Drug Interactions: Polyvalent Cation-containing Antacids:** In a clinical trial, co-  
463 administration of 75 mg of PROMACTA with a polyvalent cation-containing antacid (1,524 mg  
464 aluminum hydroxide, 1,425 mg magnesium carbonate, and sodium alginate) to 26 healthy adult  
465 subjects decreased plasma eltrombopag AUC<sub>0-∞</sub> and C<sub>max</sub> by approximately 70%. The  
466 contribution of sodium alginate to this interaction is not known.

467 **Cytochrome P450 Enzymes (CYPs):** In a clinical trial, PROMACTA 75 mg once  
468 daily was administered for 7 days to 24 healthy male subjects did not show inhibition or  
469 induction of the metabolism of a combination of probe substrates for CYP1A2 (caffeine),  
470 CYP2C19 (omeprazole), CYP2C9 (flurbiprofen), or CYP3A4 (midazolam) in humans. Probe  
471 substrates for CYP2C8 were not evaluated in this trial.

472 **Rosuvastatin:** In a clinical trial, co-administration of 75 mg of PROMACTA once  
473 daily for 5 days with a single 10 mg dose of the OATP1B1 and BCRP substrate, rosuvastatin to  
474 39 healthy adult subjects increased plasma rosuvastatin AUC<sub>0-∞</sub> by 55% and C<sub>max</sub> by 103%.

475 **Lopinavir/Ritonavir:** In a clinical trial, co-administration of repeat dose lopinavir 400  
476 mg /ritonavir 100 mg twice daily with a single dose of PROMACTA 100 mg to 40 healthy adult  
477 subjects decreased plasma eltrombopag AUC<sub>0-∞</sub> by 17%.

478 **Pegylated Interferon alfa-2a + Ribavirin and Pegylated Interferon alfa-2b +**  
479 **Ribavirin:** The pharmacokinetics of eltrombopag in both the presence and absence of pegylated  
480 interferon alfa 2a and 2b therapy were evaluated using a population pharmacokinetic analysis in  
481 635 patients with chronic hepatitis C. The population PK model estimates of clearance indicate  
482 no significant difference in eltrombopag clearance in the presence of pegylated interferon alfa  
483 plus ribavirin therapy.

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

488 **Specific Populations: Ethnicity:** Based on two population PK analyses of eltrombopag  
489 concentrations in ITP and chronic hepatitis C patients, East Asian (i.e., Japanese, Chinese,  
490 Taiwanese, and Korean) subjects exhibited 50 to 55% higher eltrombopag plasma concentrations  
491 compared to non-East Asian subjects [*see Dosage and Administration (2.1)*]. An

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

495 *Hepatic Impairment:* In a pharmacokinetic trial, the disposition of a single 50 mg  
496 dose of PROMACTA in patients with mild, moderate, and severe hepatic impairment was  
497 compared to subjects with normal hepatic function. The degree of hepatic impairment was based  
498 on Child-Pugh score. Plasma eltrombopag  $AUC_{0-\infty}$  was 41% higher in patients with mild hepatic  
499 impairment (Child-Pugh Class A) compared to subjects with normal hepatic function. Plasma  
500 eltrombopag  $AUC_{0-\infty}$  was approximately 2-fold higher in patients with moderate (Child-Pugh  
501 Class B) and severe hepatic impairment (Child-Pugh Class C). The half-life of eltrombopag was  
502 prolonged 2-fold in these patients. This clinical trial did not evaluate protein binding effects.

503 *Chronic Liver Disease:* A population PK analysis in thrombocytopenic patients with  
504 chronic liver disease following repeat doses of eltrombopag demonstrated that mild hepatic  
505 impairment resulted in an 87% to 110% higher plasma eltrombopag  $AUC_{(0-\tau)}$  and patients with  
506 moderate hepatic impairment had approximately 141% to 240% higher plasma eltrombopag  
507  $AUC_{(0-\tau)}$  values compared to patients with normal hepatic function. The half-life of eltrombopag  
508 was prolonged 3-fold in patients with mild hepatic impairment and 4-fold in patients with  
509 moderate hepatic impairment. This clinical trial did not evaluate protein binding effects.

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

516 *Renal Impairment:* The disposition of a single 50 mg dose of PROMACTA in  
517 patients with mild (creatinine clearance (CrCl) of 50 to 80 mL/min), moderate (CrCl of 30 to 49  
518 mL/min), and severe (CrCl less than 30 mL/min) renal impairment was compared to subjects  
519 with normal renal function. Average total plasma eltrombopag  $AUC_{0-\infty}$  was 32% to 36% lower in  
520 subjects with mild to moderate renal impairment and 60% lower in subjects with severe renal  
521 impairment compared with healthy subjects. The effect of renal impairment on unbound (active)  
522 eltrombopag exposure has not been assessed.

## 523 **12.6 Assessment of Risk of QT/QTc Prolongation**

524 There is no indication of a QT/QTc prolonging effect of PROMACTA at doses up to  
525 150 mg daily for 5 days. The effects of PROMACTA at doses up to 150 mg daily for 5 days  
526 (supratherapeutic doses) on the QT/QTc interval was evaluated in a double-blind, randomized,  
527 placebo- and positive-controlled (moxifloxacin 400 mg, single oral dose) crossover trial in  
528 healthy adult subjects. Assay sensitivity was confirmed by significant QTc prolongation by  
529 moxifloxacin.

530 **13 NONCLINICAL TOXICOLOGY**

531 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

534 Eltrombopag was not carcinogenic in mice at doses up to 75 mg/kg/day or in rats at doses  
535 up to 40 mg/kg/day (exposures up to 4 times the human clinical exposure based on AUC in ITP  
536 patients at 75 mg/day and 2 times the human clinical exposure based on AUC in chronic hepatitis  
537 C patients at 100 mg/day).

538 Eltrombopag was not mutagenic or clastogenic in a bacterial mutation assay or in 2 *in*  
539 *vivo* assays in rats (micronucleus and unscheduled DNA synthesis, 10 times the human clinical  
540 exposure based on C<sub>max</sub> in ITP patients at 75 mg/day and 7 times the human clinical exposure  
541 based on C<sub>max</sub> in chronic hepatitis C patients at 100 mg/day). In the *in vitro* mouse lymphoma  
542 assay, eltrombopag was marginally positive (<3-fold increase in mutation frequency).

543 Eltrombopag did not affect female fertility in rats at doses up to 20 mg/kg/day (2 times  
544 the human clinical exposure based on AUC in ITP patients at 75 mg/day and similar to the  
545 human clinical exposure based on AUC in chronic hepatitis C patients at 100 mg/day).  
546 Eltrombopag did not affect male fertility in rats at doses up to 40 mg/kg/day, the highest dose  
547 tested (3 times the human clinical exposure based on AUC in ITP patients at 75 mg/day and 2  
548 times the human clinical exposure based on AUC in chronic hepatitis C patients at 100 mg/day).

549 **13.2 Animal Pharmacology/Toxicology**

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

552 Treatment-related cataracts were detected in rodents in a dose- and time-dependent  
553 manner. At  $\geq 6$  times the human clinical exposure based on AUC in ITP patients at 75 mg/day  
554 and 3 times the human clinical exposure based on AUC in chronic hepatitis C patients at 100  
555 mg/day, cataracts were observed in mice after 6 weeks and in rats after 28 weeks of dosing. At  
556  $\geq 4$  times the human clinical exposure based on AUC in ITP patients at 75 mg/day and 2 times  
557 the human clinical exposure based on AUC in chronic hepatitis C patients at 100 mg/day,  
558 cataracts were observed in mice after 13 weeks and in rats after 39 weeks of dosing [*see*  
559 *Warnings and Precautions (5.6)*].

560 Renal tubular toxicity was observed in studies up to 14 days in duration in mice and rats  
561 at exposures that were generally associated with morbidity and mortality. Tubular toxicity was  
562 also observed in a 2-year oral carcinogenicity study in mice at doses of 25, 75, and  
563 150 mg/kg/day. The exposure at the lowest dose was 1.2 times the human clinical exposure  
564 based on AUC in ITP patients at 75 mg/day and 0.6 times the human clinical exposure based on  
565 AUC in chronic hepatitis C patients at 100 mg/day. No similar effects were observed in mice  
566 after 13 weeks at exposures greater than those associated with renal changes in the 2-year study,  
567 suggesting that this effect is both dose- and time-dependent.

568 **14 CLINICAL STUDIES**

569 **14.1 Chronic ITP**

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

573 Trials 1 and 2: In trials 1 and 2, patients who had completed at least one prior ITP  
574 therapy and who had a platelet count  $<30 \times 10^9/L$  were randomized to receive either  
575 PROMACTA or placebo daily for up to 6 weeks, followed by 6 weeks off therapy. During the  
576 trials, PROMACTA or placebo was discontinued if the platelet count exceeded  $200 \times 10^9/L$ . The  
577 primary efficacy endpoint was response rate, defined as a shift from a baseline platelet count of  
578  $<30 \times 10^9/L$  to  $\geq 50 \times 10^9/L$  at any time during the treatment period.

579 The median age of the patients was 50 years and 60% were female. Approximately 70%  
580 of the patients had received at least 2 prior ITP therapies (predominantly corticosteroids,  
581 immunoglobulins, rituximab, cytotoxic therapies, danazol, and azathioprine) and 40% of the  
582 patients had undergone splenectomy. The median baseline platelet counts (approximately  $18 \times$   
583  $10^9/L$ ) were similar among all treatment groups.

584 Trial 1 randomized 114 patients (2:1) to PROMACTA 50 mg or placebo. Trial 2  
585 randomized 117 patients (1:1:1:1) among placebo or 1 of 3 dose regimens of PROMACTA,  
586 30 mg, 50 mg, or 75 mg each administered daily.

587 Table 6 shows for each trial the primary efficacy outcomes for the placebo groups and the  
588 patient groups who received the 50 mg daily regimen of PROMACTA.

589  
590 **Table 6. Trials 1 and 2 Platelet Count Response ( $\geq 50 \times 10^9/L$ ) Rates in Adults With Chronic**  
591 **Immune (Idiopathic) Thrombocytopenia**

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

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

593  
594 The platelet count response to PROMACTA was similar among patients who had or had  
595 not undergone splenectomy. In general, increases in platelet counts were detected 1 week  
596 following initiation of PROMACTA and the maximum response was observed after 2 weeks of  
597 therapy. In the placebo and 50 mg dose groups of PROMACTA, the trial drug was discontinued  
598 due to an increase in platelet counts to  $>200 \times 10^9/L$  in 3% and 27% of the patients, respectively.  
599 The median duration of treatment with the 50 mg dose of PROMACTA was 42 days in Trial 1  
600 and 43 days in Trial 2.

601 Of 7 patients who underwent hemostatic challenges, additional ITP medications were  
602 required in 3 of 3 placebo group patients and 0 of 4 patients treated with PROMACTA. Surgical

603 procedures accounted for most of the hemostatic challenges. Hemorrhage requiring transfusion  
604 occurred in one placebo group patient and no patients treated with PROMACTA.

605 **Trial 3:** In this trial, 197 patients were randomized (2:1) to receive either PROMACTA  
606 50 mg once daily (n = 135) or placebo (n = 62) for 6 months, during which time the dose of  
607 PROMACTA could be adjusted based on individual platelet counts. Patients were allowed to  
608 taper or discontinue concomitant ITP medications after being treated with PROMACTA for  
609 6 weeks. Patients were permitted to receive rescue treatments at any time during the trial as  
610 clinically indicated. The primary endpoint was the odds of achieving a platelet count  $\geq 50 \times 10^9/L$   
611 and  $\leq 400 \times 10^9/L$  for patients receiving PROMACTA relative to placebo and was based on  
612 patient response profiles throughout the 6-month treatment period.

613 The median age of the patients treated with PROMACTA and placebo was 47 years and  
614 52.5 years, respectively. Approximately half of the patients treated with PROMACTA and  
615 placebo (47% and 50%, respectively) were receiving concomitant ITP medication  
616 (predominantly corticosteroids) at randomization and had baseline platelet counts  $\leq 15 \times 10^9/L$   
617 (50% and 48%, respectively). A similar percentage of patients treated with PROMACTA and  
618 placebo (37% and 34%, respectively) had a prior splenectomy.

619 In 134 patients who completed 26 weeks of treatment, a sustained platelet response  
620 (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  
621 treatment period in the absence of rescue medication at any time) was achieved by 60% of  
622 patients treated with PROMACTA, compared to 10% of patients treated with placebo  
623 (splenectomized patients: PROMACTA 51%, placebo 8%; non-splenectomized patients:  
624 PROMACTA 66%, placebo 11%). The proportion of responders in the PROMACTA treatment  
625 group was between 37% and 56% compared to 7% and 19% in the placebo treatment group for  
626 all on-therapy visits. Patients treated with PROMACTA were significantly more likely to  
627 achieve a platelet count between  $50 \times 10^9/L$  and  $400 \times 10^9/L$  during the entire 6-month treatment  
628 period compared to those patients treated with placebo.

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

630

631 **Table 7. Outcomes of Treatment from Trial 3 in Adults With Chronic Immune (Idiopathic)**  
632 **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)

633

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

637 **Extension Trial:** Patients who completed any prior clinical trial with PROMACTA were  
638 enrolled in an open-label, single-arm trial in which attempts were made to decrease the dose or

639 eliminate the need for any concomitant ITP medications. PROMACTA was administered to 299  
640 patients; 249 completed 6 months, 210 patients completed 12 months, and 138 patients  
641 completed 24 months of therapy. The median baseline platelet count was  $19 \times 10^9/L$  prior to  
642 administration of PROMACTA.

#### 643 **14.2 Chronic Hepatitis C-Associated Thrombocytopenia**

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

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

673 In both trials, a significantly greater proportion of patients treated with PROMACTA  
674 achieved SVR (see Table 8). The improvement in the proportion of patients who achieved SVR  
675 was consistent across subgroups based on baseline platelet count ( $<50 \times 10^9/L$  versus  $\geq 50 \times$   
676  $10^9/L$ ). In patients with high baseline viral loads ( $\geq 800,000$ ), the SVR rate was 18% (82/452) for  
677 PROMACTA versus 8% (20/239) for placebo.

678

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

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

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

683 <sup>b</sup> PROMACTA given in peginterferon alfa-2b (1.5 mcg/kg once weekly for 48 weeks for genotypes  
684 1/4/6; 24 weeks for genotype 2 or 3) plus ribavirin (800 to 1,400 mg daily in 2 divided doses orally).

685 <sup>c</sup> Target platelet count was  $\geq 90 \times 10^9/L$  for Trial 1 and  $\geq 100 \times 10^9/L$  for Trial 2.

686 <sup>d</sup> *P* value <0.05 for PROMACTA versus placebo.

687

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

## 691 **16 HOW SUPPLIED/STORAGE AND HANDLING**

- 692 • The 12.5 mg tablets are round, biconvex, white, film-coated tablets debossed with GS MZ1  
693 and 12.5 on one side and are available in bottles of 30: NDC 0007-4643-13.
- 694 • The 25 mg tablets are round, biconvex, orange, film-coated tablets debossed with GS NX3  
695 and 25 on one side and are available in bottles of 30: NDC 0007-4640-13.
- 696 • The 50 mg tablets are round, biconvex, blue, film-coated tablets debossed with GS UFU and  
697 50 on one side and are available in bottles of 30: NDC 0007-4641-13.
- 698 • The 75 mg tablets are round, biconvex, pink, film-coated tablets debossed with GS FFS  
699 and 75 on one side and are available in bottles of 30: NDC 0007-4642-13.
- 700 • The 100 mg tablets are round, biconvex, green, film-coated tablets debossed with GS 1L5  
701 and 100 on one side and are available in bottles of 30: NDC 0007-4644-13. This product  
702 contains a desiccant.

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

706 **17 PATIENT COUNSELING INFORMATION**

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

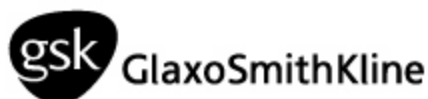
708 Prior to treatment, patients should fully understand and be informed of the following risks  
709 and considerations for PROMACTA:

- 710 • For patients with ITP, therapy with PROMACTA is administered to achieve and maintain a  
711 platelet count  $\geq 50 \times 10^9/L$  as necessary to reduce the risk for bleeding,
- 712 • For patients with chronic hepatitis C, therapy with PROMACTA is administered to achieve  
713 and maintain a platelet count necessary to initiate and maintain antiviral therapy with  
714 pegylated interferon and ribavirin.
- 715 • Therapy with PROMACTA may be associated with hepatobiliary laboratory abnormalities.
- 716 • Advise patients with chronic hepatitis C and cirrhosis that they may be at risk for hepatic  
717 decompensation when receiving alfa interferon therapy.
- 718 • Advise patients that they should report any of the following signs and symptoms of liver  
719 problems to their healthcare provider right away.
  - 720 • yellowing of the skin or the whites of the eyes (jaundice)
  - 721 • unusual darkening of the urine
  - 722 • unusual tiredness
  - 723 • right upper stomach area pain
- 724 • Advise patients that thrombocytopenia and risk of bleeding may reoccur upon discontinuing  
725 PROMACTA, particularly if PROMACTA is discontinued while the patient is on  
726 anticoagulants or antiplatelet agents.
- 727 • Advise patients that too much PROMACTA may result in excessive platelet counts and a risk  
728 for thrombotic/thromboembolic complications.
- 729 • Advise patients that during therapy with PROMACTA, they should continue to avoid  
730 situations or medications that may increase the risk for bleeding.
- 731 • Advise patients to have a baseline ocular examination prior to administration of  
732 PROMACTA and be monitored for signs and symptoms of cataracts during therapy.
- 733 • Advise patients to keep at least a 4-hour interval between PROMACTA and foods, mineral  
734 supplements, and antacids which contain polyvalent cations such as iron, calcium, aluminum,  
735 magnesium, selenium, and zinc.

736

737 PROMACTA is a registered trademark of GlaxoSmithKline. The following are registered  
738 trademarks of their respective owners: PEGASYS/Hoffmann-La Roche Inc.;  
739 PEGINTRON/Schering Corporation; FibroSURE/Laboratory Corporation of America Holdings.

740



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742 GlaxoSmithKline

743 Research Triangle Park, NC 27709

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## 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.

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

42

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

45

46 PROMACTA is not used to make your platelet count normal.

47

48

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

52

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

55

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

57

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

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

- 60       • have liver or kidney problems  
61       • have or had a blood clot  
62       • have a history of cataracts  
63       • have had surgery to remove your spleen (splenectomy)  
64       • have a bone marrow problem  
65       • have bleeding problems  
66       • are Asian and you are of Chinese, Japanese, Taiwanese, or Korean ancestry, you  
67       may need a lower dose of PROMACTA.  
68       • have any other medical conditions  
69       • are pregnant or plan to become pregnant. It is not known if PROMACTA will  
70       harm an unborn baby.

71       ***Pregnancy Registry:*** There is a registry for women who become pregnant  
72       during treatment with PROMACTA. If you become pregnant, consider this  
73       registry. The purpose of the registry is to collect safety information about the  
74       health of you and your baby. Contact the registry as soon as you become aware  
75       of the pregnancy, or ask your healthcare provider to contact the registry for  
76       you. You and your healthcare provider can get information and enroll in the  
77       registry by calling 1-888-825-5249.

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

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

81

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

86

87 Especially tell your healthcare provider if you take:

- 88 • certain medicines used to treat high cholesterol, called “statins”.
- 89 • a blood thinner medicine.

90

91 Certain medicines may keep PROMACTA from working correctly. Take PROMACTA  
92 either 4 hours before or 4 hours after taking these products:

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

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

98

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

101

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

- 103 • Take PROMACTA exactly as your healthcare provider tells you. Do not stop  
104 taking PROMACTA without talking with your healthcare provider first. Do not  
105 change your dose or schedule for taking PROMACTA unless your healthcare  
106 provider tells you to change it.
- 107 • Take PROMACTA on an empty stomach, either 1 hour before or 2 hours after  
108 eating food.
- 109 • Take PROMACTA at least 4 hours before or 4 hours after eating dairy products  
110 and calcium fortified juices.
- 111 • If you miss a dose of PROMACTA, wait and take your next scheduled dose. Do  
112 not take more than one dose of PROMACTA in one day.
- 113 • If you take too much PROMACTA, you may have a higher risk of serious side  
114 effects. Call your healthcare provider right away.
- 115 • Your healthcare provider will check your platelet count every week and change  
116 your dose of PROMACTA as needed. This will happen every week until your  
117 healthcare provider decides that your dose of PROMACTA can stay the same.  
118 After that, you will need to have blood tests every month. When you stop taking

119 PROMACTA, you will need to have blood tests for at least 4 weeks to check if  
120 your platelet count drops too low.

- 121 • Tell your healthcare provider about any bruising or bleeding that happens while  
122 you take and after you stop taking PROMACTA.

123

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

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

126

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

128 PROMACTA may cause serious side effects, including:

129

- 130 • See **“What is the most important information I should know  
131 about PROMACTA?”**
- 132 • **Bone marrow changes (increased reticulin and possible bone  
133 marrow fibrosis).** Long-term use of PROMACTA may cause changes in  
134 your bone marrow. These changes may lead to abnormal blood cells or your  
135 body making less blood cells. The mild form of these bone marrow changes  
136 is called “increased reticulin” which may progress to a more severe form  
137 called “fibrosis”. The mild form may cause no problems while the severe  
138 form may cause life-threatening blood problems. Signs of bone marrow  
139 changes may show up as abnormal results in your blood tests. Your  
140 healthcare provider will decide if abnormal blood test results mean that you  
141 should have bone marrow tests or if you should stop taking PROMACTA.
- 142 • **High platelet counts and higher risk for blood clots.** Your risk of getting  
143 a blood clot is increased if your platelet count is too high during treatment  
144 with PROMACTA. Your risk of getting a blood clot may also be increased  
145 during treatment with PROMACTA if you have normal or low platelet counts.  
146 You may have severe problems or die from some forms of blood clots, such  
147 as clots that travel to the lungs or that cause heart attacks or strokes. Your  
148 healthcare provider will check your blood platelet counts, and change your  
149 dose or stop PROMACTA if your platelet counts get too high. Tell your  
150 healthcare provider right away if you have signs and symptoms of a blood  
151 clot in the leg, such as swelling, pain, or tenderness in your leg.  
152 People with chronic liver disease may be at risk for a type of blood clot in  
153 the stomach area. Stomach area pain may be a symptom of this type of  
154 blood clot.
- 155 • **New or worsened cataracts (a clouding of the lens in the eye).** New  
156 or worsened cataracts have happened in people taking PROMACTA. Your  
157 healthcare provider will check your eyes before and during your treatment

158 with PROMACTA. Tell your healthcare provider about any changes in your  
159 eyesight while taking PROMACTA.

160

161 The most common side effects of PROMACTA when used to treat chronic ITP are:

- 162 • nausea
- 163 • diarrhea
- 164 • upper respiratory tract infection. Symptoms may include runny nose, stuffy  
165 nose, and sneezing
- 166 • vomiting
- 167 • muscle aches
- 168 • urinary tract infections. Symptoms may include frequent or urgent need to  
169 urinate, low fever in some people, pain or burning with urination
- 170 • pain or swelling (inflammation) in your throat or mouth (oropharyngeal pain and  
171 pharyngitis)
- 172 • abnormal liver function tests
- 173 • back pain
- 174 • “flu” like symptoms (influenza) including fever, headache, tiredness, cough, sore  
175 throat, and body aches
- 176 • skin tingling, itching, or burning
- 177 • rash

178

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

- 181 • low red blood cell count (anemia)
- 182 • fever
- 183 • tiredness
- 184 • headache
- 185 • nausea
- 186 • diarrhea
- 187 • decreased appetite
- 188 • “flu” like symptoms (influenza) including fever, headache, tiredness, cough, sore  
189 throat, and body aches
- 190 • feeling weak
- 191 • trouble sleeping
- 192 • cough
- 193 • itching
- 194 • chills
- 195 • muscle aches
- 196 • hair loss
- 197 • swelling in your ankles, feet, and legs

198

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

202

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

205

### 206 **How should I store PROMACTA Tablets?**

- 207 • Store at room temperature between 68°F to 77°F (20°C to 25°C).
- 208 • Keep PROMACTA tightly closed in the bottle given to you.
- 209 • The PROMACTA bottle may contain a desiccant pack to help keep your medicine  
210 dry. Do not remove the desiccant pack from the bottle.
- 211 • **Keep PROMACTA and all medicines out of the reach of children.**

212

### 213 **General information about the safe and effective use of PROMACTA**

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

218

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

223

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

225

### 226 **What are the ingredients in PROMACTA?**

227 Active ingredient: eltrombopag olamine.

228 Inactive ingredients:

- 229 • Tablet Core: magnesium stearate, mannitol, microcrystalline cellulose, povidone,  
230 and sodium starch glycolate.
- 231 • Coating: hypromellose, polyethylene glycol 400, titanium dioxide, polysorbate  
232 80 (12.5 mg tablet), and FD&C Yellow No. 6 aluminum lake (25 mg tablet),  
233 FD&C Blue No. 2 aluminum lake (50 mg tablet), Iron Oxide Red and Iron Oxide  
234 Black (75 mg tablet), or Iron Oxide Yellow and Iron Oxide Black (100 mg  
235 tablet).

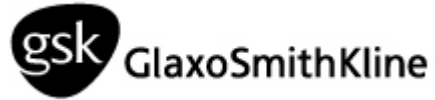
236

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

239

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241



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244 Research Triangle Park, NC 27709

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248 Revised: November 2012

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