

## 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 HEPATIC DECOMPENSATION IN PATIENTS WITH CHRONIC HEPATITIS C

See full prescribing information for complete boxed warning

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

### RECENT MAJOR CHANGES

Boxed Warning	02/2014
Indications and Usage, Treatment of Severe Aplastic Anemia (1.3)	08/2014
Indications and Usage, Limitations of Use (1.4)	04/2014
Dosage and Administration, Severe Aplastic Anemia (2.3)	08/2014
Warnings and Precautions, Hepatic Decompensation in Patients with Chronic Hepatitis C (5.1)	02/2014
Warnings and Precautions, Hepatotoxicity (5.2)	02/2014
Warnings and Precautions, Bone Marrow Reticulin Formation removal (formerly 5.3)	02/2014
Warnings and Precautions, Laboratory Monitoring removal (formerly 5.5)	02/2014

### 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)
- thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. (1.2)
- patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy. (1.3)

Limitations of Use:

- PROMACTA should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding. (1.4)
- 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. (1.4)
- Safety and efficacy have not been established in combination with direct-acting antiviral agents used without interferon for treatment of chronic hepatitis C infection. (1.4)

### DOSAGE AND ADMINISTRATION

- Take on an empty stomach (1 hour before or 2 hours after a meal). (2.4)
- 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). (2.4)

- Chronic ITP:** Initiate PROMACTA at 50 mg once daily for most patients. Reduce initial dose in patients with hepatic impairment and/or patients of East Asian ancestry. Adjust to maintain platelet count greater than or equal to  $50 \times 10^9/L$ . 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 target platelet count required to initiate antiviral therapy. Do not exceed a daily dose of 100 mg. (2.2)
- Severe Aplastic Anemia:** Initiate PROMACTA at 50 mg once daily for most patients. Reduce initial dose in patients with hepatic impairment or patients of East Asian ancestry. Adjust to maintain platelet count greater than  $50 \times 10^9/L$ . Do not exceed 150 mg per day. (2.3)

### DOSAGE FORMS AND STRENGTHS

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

### CONTRAINDICATIONS

None. (4)

### WARNINGS and PRECAUTIONS

- Hepatic Decompensation in Patients with Chronic Hepatitis C. (5.1)
- Hepatotoxicity: Monitor liver function before and during therapy. (5.2)
- Thrombotic/Thromboembolic Complications: Portal vein thrombosis has been reported in patients with chronic liver disease receiving PROMACTA. Monitor platelet counts regularly. (5.3)

### ADVERSE REACTIONS

- The most common adverse reactions in ITP patients (greater than or equal to 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 (greater than or equal to 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. (6.1)
- The most common adverse reactions in patients with severe aplastic anemia (greater than or equal to 20%) were: nausea, fatigue, cough, diarrhea, and headache. (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

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. (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 chronic ITP patients with hepatic impairment. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2014

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## FULL PRESCRIBING INFORMATION

### **WARNING: RISK FOR HEPATIC DECOMPENSATION IN PATIENTS WITH CHRONIC HEPATITIS C**

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

## **1 INDICATIONS AND USAGE**

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

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

### **1.2 Treatment of Thrombocytopenia in Patients with Hepatitis C Infection**

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

### **1.3 Treatment of Severe Aplastic Anemia**

PROMACTA is indicated for the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.

### **1.4 Limitations of Use**

- 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 used without interferon for treatment of chronic hepatitis C infection.

## **2 DOSAGE AND ADMINISTRATION**

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

Use the lowest dose of PROMACTA to achieve and maintain a platelet count greater than or equal to  $50 \times 10^9/L$  as necessary to reduce the risk for bleeding. Dose adjustments are based upon the platelet count response. Do not use PROMACTA to normalize platelet counts [see *Warnings and Precautions (5.3)*]. In clinical trials, platelet counts generally increased within 1 to 2 weeks after starting PROMACTA and decreased within 1 to 2 weeks after discontinuing PROMACTA [see *Clinical Studies (14.1)*].

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

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

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

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

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

51

52 **Table 1. Dose Adjustments of PROMACTA in Adults with Chronic Immune (Idiopathic)**  
53 **Thrombocytopenia**

Platelet Count Result	Dose Adjustment or Response
$<50 \times 10^9/L$ following at least 2 weeks of PROMACTA	Increase daily dose by 25 mg to a maximum of 75 mg/day. For patients taking 12.5 mg once daily, increase the dose to 25 mg daily before increasing the dose amount by 25 mg.
$\geq 200 \times 10^9/L$ to $\leq 400 \times 10^9/L$ at any time	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
$>400 \times 10^9/L$	Stop PROMACTA; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is $<150 \times 10^9/L$ , 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.

54

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

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

60            **Discontinuation:** Discontinue PROMACTA if the platelet count does not increase to a  
61 level sufficient to avoid clinically important bleeding after 4 weeks of therapy with  
62 PROMACTA at the maximum daily dose of 75 mg. Excessive platelet count responses, as  
63 outlined in Table 1, or important liver test abnormalities also necessitate discontinuation of  
64 PROMACTA [*see Warnings and Precautions (5.2)*]. Obtain CBCs with differentials, including  
65 platelet counts, weekly for at least 4 weeks following discontinuation of PROMACTA.

66            **2.2 Chronic Hepatitis C-associated Thrombocytopenia**

67            Use the lowest dose of PROMACTA to achieve and maintain a platelet count necessary  
68 to initiate and maintain antiviral therapy with pegylated interferon and ribavirin. Dose  
69 adjustments are based upon the platelet count response. Do not use PROMACTA to normalize  
70 platelet counts [*see Warnings and Precautions (5.3)*]. In clinical trials, platelet counts generally  
71 began to rise within the first week of treatment with PROMACTA [*see Clinical Studies (14.2)*].

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

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

76            During antiviral therapy, adjust the dose of PROMACTA to avoid dose reductions of  
77 peginterferon. Monitor CBCs with differentials, including platelet counts, weekly during  
78 antiviral therapy until a stable platelet count is achieved. Monitor platelet counts monthly  
79 thereafter. Do not exceed a dose of 100 mg daily. Monitor clinical hematology and liver tests  
80 regularly throughout therapy with PROMACTA.

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

83

84 **Table 2. Dose Adjustments of PROMACTA in Adults with Thrombocytopenia due to**  
85 **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, reinitiate therapy at a daily dose reduced by 25 mg. For patients taking 25 mg once daily, reinitiate therapy at a daily dose of 12.5 mg.
>400 x 10 <sup>9</sup> /L after 2 weeks of therapy at lowest dose of PROMACTA	Discontinue PROMACTA.

86

87 **Discontinuation:** The prescribing information for pegylated interferon and ribavirin  
88 include recommendations for antiviral treatment discontinuation for treatment futility. Refer to  
89 pegylated interferon and ribavirin prescribing information for discontinuation recommendations  
90 for antiviral treatment futility.

91 PROMACTA should be discontinued when antiviral therapy is discontinued. Excessive  
92 platelet count responses, as outlined in Table 2, or important liver test abnormalities also  
93 necessitate discontinuation of PROMACTA [see *Warnings and Precautions (5.2)*].

### 94 **2.3 Severe Aplastic Anemia**

95 Use the lowest dose of PROMACTA to achieve and maintain a hematologic response.  
96 Dose adjustments are based upon the platelet count. Hematologic response requires dose  
97 titration, generally up to 150 mg, and may take up to 16 weeks after starting PROMACTA [see  
98 *Clinical Studies (14.3)*].

99 **Initial Dose Regimen:** Initiate PROMACTA at a dose of 50 mg once daily.

100 For severe aplastic anemia in patients of East Asian ancestry or those with mild,  
101 moderate, or severe hepatic impairment (Child-Pugh Class A, B, C), initiate PROMACTA at a  
102 reduced dose of 25 mg once daily [see *Use in Specific Populations (8.8)(8.6)*, *Clinical*  
103 *Pharmacology (12.3)*].

104 **Monitoring and Dose Adjustment:** Adjust the dose of PROMACTA in 50 mg  
105 increments every 2 weeks as necessary to achieve the target platelet count greater than or equal  
106 to 50 x 10<sup>9</sup>/L as necessary. Do not exceed a dose of 150 mg daily. Monitor clinical hematology  
107 and liver tests regularly throughout therapy with PROMACTA and modify the dosage regimen  
108 of PROMACTA based on platelet counts as outlined in Table 3.

109

110 **Table 3. Dose Adjustments of PROMACTA in Patients with Severe Aplastic Anemia**

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 50 mg to a maximum of 150 mg/day. For patients taking 25 mg once daily, increase the dose to 50 mg daily before increasing the dose amount by 50 mg.
≥200 x 10 <sup>9</sup> /L to ≤400 x 10 <sup>9</sup> /L at any time	Decrease the daily dose by 50 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
>400 x 10 <sup>9</sup> /L	Stop PROMACTA for 1 week. Once the platelet count is <150 x 10 <sup>9</sup> /L, reinstitute therapy at a dose reduced by 50 mg.
>400 x 10 <sup>9</sup> /L after 2 weeks of therapy at lowest dose of PROMACTA	Discontinue PROMACTA.

111

112 For patients who achieve tri-lineage response, including transfusion independence,  
113 lasting at least 8 weeks: the dose of PROMACTA may be reduced by 50% [*see Clinical Studies*  
114 (*14.3*)]. If counts remain stable after 8 weeks at the reduced dose, then discontinue PROMACTA  
115 and monitor blood counts. If platelet counts drop to less than 30 x 10<sup>9</sup>/L, hemoglobin to less than  
116 9 g/dL, or ANC to less than 0.5 x 10<sup>9</sup>/L, PROMACTA may be reinitiated at the previous  
117 effective dose.

118 **Discontinuation:** If no hematologic response has occurred after 16 weeks of therapy with  
119 PROMACTA, discontinue therapy. If new cytogenetic abnormalities are observed, consider  
120 discontinuation of PROMACTA [*see Adverse Reactions (6.1)*]. Excessive platelet count  
121 responses (as outlined in Table 3) or important liver test abnormalities also necessitate  
122 discontinuation of PROMACTA [*see Warnings and Precautions (5.2)*].

## 123 **2.4 Administration**

124 Take PROMACTA on an empty stomach (1 hour before or 2 hours after a meal) [*see*  
125 *Clinical Pharmacology (12.3)*].

126 Allow at least a 4-hour interval between PROMACTA and other medications (e.g.,  
127 antacids), calcium-rich foods (e.g., dairy products and calcium fortified juices), or supplements  
128 containing polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, and zinc  
129 [*see Drug Interactions (7.1)*].

## 130 **3 DOSAGE FORMS AND STRENGTHS**

- 131 • 12.5 mg tablets — round, biconvex, white, film-coated tablets debossed with GS MZ1 and  
132 12.5 on one side. Each tablet, for oral administration, contains eltrombopag olamine,  
133 equivalent to 12.5 mg of eltrombopag free acid.

- 134 • 25 mg tablets — round, biconvex, orange, film-coated tablets debossed with GS NX3 and  
135 25 on one side. Each tablet, for oral administration, contains eltrombopag olamine,  
136 equivalent to 25 mg of eltrombopag free acid.
- 137 • 50 mg tablets — round, biconvex, blue, film-coated tablets debossed with GS UFU and 50 on  
138 one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to  
139 50 mg of eltrombopag free acid.
- 140 • 75 mg tablets — round, biconvex, pink, film-coated tablets debossed with GS FFS and 75 on  
141 one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to  
142 75 mg of eltrombopag free acid.
- 143 • 100 mg tablets — round, biconvex, green, film-coated tablets debossed with GS 1L5. Each  
144 tablet, for oral administration, contains eltrombopag olamine, equivalent to 100 mg of  
145 eltrombopag free acid.

#### 146 **4 CONTRAINDICATIONS**

147 None.

#### 148 **5 WARNINGS AND PRECAUTIONS**

##### 149 **5.1 Hepatic Decompensation in Patients with Chronic Hepatitis C**

150 In patients with chronic hepatitis C, PROMACTA in combination with interferon and  
151 ribavirin may increase the risk of hepatic decompensation. In two controlled clinical trials in  
152 patients with chronic hepatitis C and thrombocytopenia, ascites and encephalopathy occurred  
153 more frequently on the arm receiving treatment with PROMACTA plus antivirals (7%) than the  
154 placebo plus antivirals arm (4%). Patients with low albumin levels (less than 3.5 g/dL) or Model  
155 for End-Stage Liver Disease (MELD) score greater than or equal to 10 at baseline had a greater  
156 risk for hepatic decompensation on the arm receiving treatment with PROMACTA plus  
157 antivirals. Discontinue PROMACTA if antiviral therapy is discontinued.

##### 158 **5.2 Hepatotoxicity**

159 PROMACTA can cause liver enzyme elevations [*see Adverse Reactions (6.1)*]. Measure  
160 serum ALT, AST, and bilirubin prior to initiation of PROMACTA, every 2 weeks during the  
161 dose adjustment phase, and monthly following establishment of a stable dose. PROMACTA  
162 inhibits UGT1A1 and OATP1B1, which may lead to indirect hyperbilirubinemia. If bilirubin is  
163 elevated, perform fractionation. Evaluate abnormal serum liver tests with repeat testing within 3  
164 to 5 days. If the abnormalities are confirmed, monitor serum liver tests weekly until resolved or  
165 stabilized. Discontinue PROMACTA if ALT levels increase to greater than or equal to 3X ULN  
166 in patients with normal liver function or greater than or equal to 3X baseline in patients with pre-  
167 treatment elevations in transaminases and are:

- 168 • progressively increasing, or  
169 • persistent for greater than or equal to 4 weeks, or  
170 • accompanied by increased direct bilirubin, or  
171 • accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation.

172 If the potential benefit for reinitiating treatment with PROMACTA is considered to  
173 outweigh the risk for hepatotoxicity, then consider cautiously reintroducing PROMACTA and  
174 measure serum liver tests weekly during the dose adjustment phase. Hepatotoxicity may reoccur  
175 if PROMACTA is reinitiated. If liver tests abnormalities persist, worsen or recur, then  
176 permanently discontinue PROMACTA.

### 177 **5.3 Thrombotic/Thromboembolic Complications**

178 In 2 controlled clinical trials in patients with chronic hepatitis C and thrombocytopenia,  
179 3% (31/955) treated with PROMACTA experienced a thrombotic event compared with 1%  
180 (5/484) on placebo. The majority of events were of the portal venous system (1% in patients  
181 treated with PROMACTA versus less than 1% for placebo).

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

185 Consider the potential for an increased risk of thromboembolism when administering  
186 PROMACTA to patients with known risk factors for thromboembolism (e.g., Factor V Leiden,  
187 ATIII deficiency, antiphospholipid syndrome, chronic liver disease). To minimize the risk for  
188 thrombotic/thromboembolic complications, do not use PROMACTA in an attempt to normalize  
189 platelet counts. Follow the dose adjustment guidelines to achieve and maintain target platelet  
190 counts [*see Dosage and Administration (2.1, 2.2, 2.3)*].

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

### 203 **5.4 Cataracts**

204 In the 3 controlled clinical trials in chronic ITP, cataracts developed or worsened in 15  
205 (7%) patients who received 50 mg PROMACTA daily and 8 (7%) placebo-group patients. In the  
206 extension trial, cataracts developed or worsened in 4% of patients who underwent ocular  
207 examination prior to therapy with PROMACTA. In the 2 controlled clinical trials in patients with  
208 chronic hepatitis C and thrombocytopenia, cataracts developed or worsened in 8% patients  
209 treated with PROMACTA and 5% patients treated with placebo.

210 Cataracts were observed in toxicology studies of eltrombopag in rodents [*see Nonclinical*  
211 *Toxicology (13.2)*]. Perform a baseline ocular examination prior to administration of

212 PROMACTA and, during therapy with PROMACTA, regularly monitor patients for signs and  
213 symptoms of cataracts.

## 214 **6 ADVERSE REACTIONS**

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

- 217 • Hepatic Decompensation in Patients with Chronic Hepatitis C [*see Warnings and*  
218 *Precautions (5.1)*]
- 219 • Hepatotoxicity [*see Warnings and Precautions (5.2)*]
- 220 • Thrombotic/Thromboembolic Complications [*see Warnings and Precautions (5.3)*]
- 221 • Cataracts [*see Warnings and Precautions (5.4)*]

### 222 **6.1 Clinical Trials Experience**

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

226 Chronic Immune (Idiopathic) Thrombocytopenia: In clinical trials, hemorrhage was  
227 the most common serious adverse reaction and most hemorrhagic reactions followed  
228 discontinuation of PROMACTA. Other serious adverse reactions included  
229 thrombotic/thromboembolic complications [*see Warnings and Precautions (5.3)*].

230 The data described below reflect exposure of PROMACTA to 446 patients with chronic  
231 ITP aged 18 to 85, of whom 65% were female across the ITP clinical development program  
232 including 3 placebo-controlled trials. PROMACTA was administered to 277 patients for at least  
233 6 months and 202 patients for at least 1 year.

234 Table 4 presents the most common adverse drug reactions (experienced by greater than or  
235 equal to 3% of patients receiving PROMACTA) from the 3 placebo-controlled trials, with a  
236 higher incidence in PROMACTA versus placebo.  
237

238 **Table 4. Adverse Reactions ( $\geq 3\%$ ) from Three Placebo-controlled Trials in Adults with**  
239 **Chronic Immune (Idiopathic) Thrombocytopenia**

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

240

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

244 Among 299 patients with chronic ITP who received PROMACTA in the single-arm  
245 extension trial, the adverse reactions occurred in a pattern similar to that seen in the placebo-  
246 controlled trials. Table 5 presents the most common treatment-related adverse reactions  
247 (experienced by greater than or less than 3% of patients receiving PROMACTA) from the  
248 extension trial.

249

250 **Table 5. Treatment-related Adverse Reactions ( $\geq 3\%$ ) from Extension Trial in Adults with**  
251 **Chronic Immune (Idiopathic) Thrombocytopenia**

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

252

253 In the 3 controlled chronic ITP trials, serum liver test abnormalities (predominantly  
254 Grade 2 or less in severity) were reported in 11% and 7% of patients for PROMACTA and  
255 placebo, respectively. Four patients (1%) treated with PROMACTA and three patients in the  
256 placebo group (2%) discontinued treatment due to hepatobiliary laboratory abnormalities. Seven  
257 of the patients treated with PROMACTA in the controlled trials with hepatobiliary laboratory  
258 abnormalities were re-exposed to PROMACTA in the extension trial. Six of these patients again  
259 experienced liver test abnormalities (predominantly Grade 1) resulting in discontinuation of  
260 PROMACTA in one patient. In the extension chronic ITP trial, one additional patient had  
261 PROMACTA discontinued due to liver test abnormalities (less than or equal to Grade 3).

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

265 **Chronic Hepatitis C-associated Thrombocytopenia:** In the 2 placebo-controlled  
266 trials, 955 patients with chronic hepatitis C-associated thrombocytopenia received PROMACTA.  
267 Table 6 presents the most common adverse drug reactions (experienced by greater than or equal  
268 to 10% of patients receiving PROMACTA compared with placebo).

269

270 **Table 6. Adverse Reactions ( $\geq 10\%$  and Greater than Placebo) from Two Placebo-**  
271 **controlled Trials in Adults with Chronic Hepatitis C**

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

272  
273 In the 2 controlled clinical trials in patients with chronic hepatitis C, hyperbilirubinemia  
274 was reported in 8% of patients receiving PROMACTA compared with 3% for placebo. Total  
275 bilirubin greater than or equal to 1.5 X ULN was reported in 76% and 50% of patients receiving  
276 PROMACTA and placebo, respectively. ALT or AST greater than or equal to 3X ULN was  
277 reported in 34% and 38% of patients for PROMACTA and placebo, respectively.

278 **Severe Aplastic Anemia:** In the single-arm, open-label trial, 43 patients with severe  
279 aplastic anemia received PROMACTA. Eleven patients (26%) were treated for greater than  
280 6 months and 7 patients (16%) were treated for greater than 1 year. The most common adverse  
281 reactions (greater than or equal to 20%) were nausea, fatigue, cough, diarrhea, and headache.  
282

283 **Table 7. Adverse Reactions ( $\geq 10\%$ ) from One Open-label Trial in Adults with Severe**  
284 **Aplastic Anemia**

<b>Adverse Reaction</b>	<b>PROMACTA (n = 43) (%)</b>
Nausea	33
Fatigue	28
Cough	23
Diarrhea	21
Headache	21
Pain in extremity	19
Dyspnea	14
Pyrexia	14
Dizziness	14
Oropharyngeal pain	14
Febrile neutropenia	14
Abdominal pain	12
Ecchymosis	12
Muscle spasms	12
Transaminases increased	12
Arthralgia	12
Rhinorrhea	12

285

286

287

288

In this trial, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. Eight patients had a new cytogenetic abnormality reported on therapy, including 5 patients who had complex changes in chromosome 7.

289

## **7 DRUG INTERACTIONS**

290

291

292

293

294

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

295

### **7.1 Polyvalent Cations (Chelation)**

296

297

298

299

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

300

301

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

302 significant reduction in PROMACTA absorption due to chelation [see *Dosage and*  
303 *Administration (2.4)*].

## 304 **7.2 Transporters**

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

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

## 316 **7.3 Protease Inhibitors**

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

322 Hepatitis C Virus (HCV) Protease Inhibitors: Coadministration of PROMACTA with  
323 either boceprevir or telaprevir did not affect eltrombopag or protease inhibitor exposure  
324 significantly [see *Clinical Pharmacology (12.3)*]. No dose adjustments are recommended. Drug  
325 interactions with other HCV 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 [see *Clinical Pharmacology (12.3)*].

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

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

343         Eltrombopag was administered orally to pregnant rats at 10, 20, or 60 mg/kg/day (0.8, 2,  
344 and 6 times, respectively, the human clinical exposure based on AUC in ITP patients at  
345 75 mg/day and 0.3, 1, and 3 times, respectively, the human clinical exposure based on AUC in  
346 chronic hepatitis C patients at 100 mg/day). Decreased fetal weights (6% to 7%) and a slight  
347 increase in the presence of cervical ribs were observed at the highest dose which also caused  
348 maternal toxicity. However, no evidence of major structural malformations was observed.

349         Pregnant rabbits were treated with oral eltrombopag doses of 30, 80, or 150 mg/kg/day  
350 (0.04, 0.3, and 0.5 times, respectively, the human clinical exposure based on AUC in ITP  
351 patients at 75 mg/day and 0.02, 0.1, and 0.3 times, respectively, the human clinical exposure  
352 based on AUC in chronic hepatitis C patients at 100 mg/day). No evidence of fetotoxicity,  
353 embryolethality, or teratogenicity was observed.

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

### 361 **8.3 Nursing Mothers**

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

### 366 **8.4 Pediatric Use**

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

### 368 **8.5 Geriatric Use**

369         Of the 106 patients in 2 randomized clinical trials of PROMACTA 50 mg in chronic ITP,  
370 22% were 65 years of age and over, while 9% were 75 years of age and over. In the 2  
371 randomized clinical trials of PROMACTA in patients with chronic hepatitis C and  
372 thrombocytopenia, 7% were 65 years of age and over, while fewer than 1% were 75 years of age  
373 and over. No overall differences in safety or effectiveness were observed between these patients  
374 and younger patients in the placebo-controlled trials, but greater sensitivity of some older  
375 individuals cannot be ruled out.

### 376 **8.6 Hepatic Impairment**

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

379         Reduce the initial dose of PROMACTA in patients with chronic ITP or severe aplastic  
380 anemia who also have hepatic impairment (Child-Pugh Class A, B, C) [*see Dosage and*

381 Administration (2.1) (2.3), Warnings and Precautions (5.2)]. No dosage adjustment is necessary  
382 for HCV patients with hepatic impairment [see Clinical Pharmacology (12.3)].

### 383 **8.7 Renal Impairment**

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

### 387 **8.8 Ethnicity**

388 Patients of East Asian ethnicity (i.e., Japanese, Chinese, Taiwanese, and Korean) exhibit  
389 higher eltrombopag exposures. A reduction in the initial dose of PROMACTA is recommended  
390 for ITP or severe aplastic anemia patients of East Asian ancestry and patients of East Asian  
391 ancestry with hepatic impairment (Child-Pugh Class A, B, C) [see Dosage and Administration  
392 (2.1, 2.3)]. No dose reduction is needed in patients of East Asian ethnicity with chronic hepatitis  
393 C [see Clinical Pharmacology (12.3)].

## 394 **10 OVERDOSAGE**

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

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

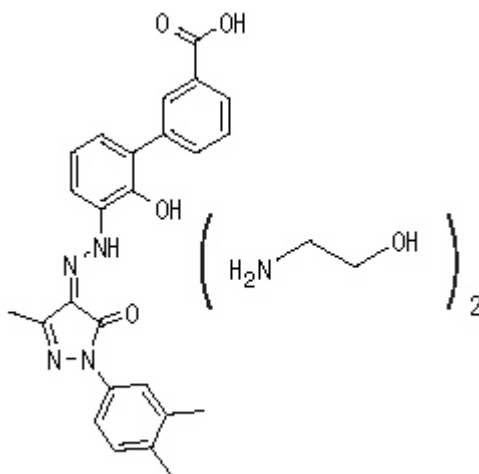
404 In case of an overdose, consider oral administration of a metal cation-containing  
405 preparation, such as calcium, aluminum, or magnesium preparations to chelate eltrombopag and  
406 thus limit absorption. Closely monitor platelet counts. Reinitiate treatment with PROMACTA in  
407 accordance with dosing and administration recommendations [see Dosage and Administration  
408 (2.1, 2.2)].

## 409 **11 DESCRIPTION**

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

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

419 olamine and 442.5 for eltrombopag free acid. Eltrombopag olamine has the following structural  
420 formula:



421  
422 Eltrombopag olamine is practically insoluble in aqueous buffer across a pH range of 1 to  
423 7.4, and is sparingly soluble in water.

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

## 431 12 CLINICAL PHARMACOLOGY

### 432 12.1 Mechanism of Action

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

### 436 12.3 Pharmacokinetics

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

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

445 **Distribution:** The concentration of eltrombopag in blood cells is approximately 50% to  
446 79% of plasma concentrations based on a radiolabel study. *In vitro* studies suggest that

447 eltrombopag is highly bound to human plasma proteins (greater than 99%). Eltrombopag is a  
448 substrate of BCRP, but is not a substrate for P-glycoprotein (P-gp) or OATP1B1.

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

454 **Elimination:** The predominant route of eltrombopag excretion is via feces (59%), and  
455 31% of the dose is found in the urine. Unchanged eltrombopag in feces accounts for  
456 approximately 20% of the dose; unchanged eltrombopag is not detectable in urine. The plasma  
457 elimination half-life of eltrombopag is approximately 21 to 32 hours in healthy subjects and 26  
458 to 35 hours in ITP patients.

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

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

469 **Rosuvastatin:** In a clinical trial, co-administration of 75 mg of PROMACTA once  
470 daily for 5 days with a single 10 mg dose of the OATP1B1 and BCRP substrate, rosuvastatin to  
471 39 healthy adult subjects increased plasma rosuvastatin AUC<sub>0-∞</sub> by 55% and C<sub>max</sub> by 103%.

472 **Protease Inhibitors: HIV Protease Inhibitors:** In a clinical trial, co-administration  
473 of repeat dose lopinavir 400 mg/ritonavir 100 mg twice daily with a single dose of PROMACTA  
474 100 mg to 40 healthy adult subjects decreased plasma eltrombopag AUC<sub>0-∞</sub> by 17%.

475 **HCV Protease Inhibitors:** In a clinical trial, co-administration of repeat dose  
476 telaprevir 750 mg every 8 hours or boceprevir 800 mg every 8 hours with a single dose of  
477 PROMACTA 200 mg to healthy adult subjects did not alter plasma telaprevir, boceprevir, or  
478 eltrombopag AUC<sub>0-∞</sub> or C<sub>max</sub> to a significant extent.

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

485 **In vitro Studies:** Eltrombopag is an inhibitor of CYP2C8 and CYP2C9 *in vitro*.  
486 Eltrombopag is an inhibitor of UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7,

487 and UGT2B15 *in vitro*. Eltrombopag is an inhibitor of the organic anion transporting polypeptide  
488 OATP1B1 and BCRP *in vitro*.

489 **Specific Populations:** *Ethnicity:* Based on two population PK analyses of eltrombopag  
490 concentrations in ITP and chronic hepatitis C patients, East Asian (i.e., Japanese, Chinese,  
491 Taiwanese, and Korean) subjects exhibited 50 to 55% higher eltrombopag plasma concentrations  
492 compared with non-East Asian subjects [*see Dosage and Administration (2.1, 2.3)*].

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

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

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

513 *Chronic Hepatitis C:* A population PK in 28 healthy adults and 635 patients with  
514 chronic hepatitis C demonstrated that patients with chronic hepatitis C treated with PROMACTA  
515 had higher plasma AUC<sub>(0-τ)</sub> values as compared with healthy subjects, and AUC<sub>(0-τ)</sub> increased  
516 with increasing Child-Pugh score. Patients with chronic hepatitis C and mild hepatic impairment  
517 had approximately 100% to 144% higher plasma AUC<sub>(0-τ)</sub> compared with healthy subjects. This  
518 clinical trial did not evaluate protein binding effects.

519 *Renal Impairment:* The disposition of a single 50 mg dose of PROMACTA in  
520 patients with mild [creatinine clearance (CrCl) of 50 to 80 mL/min], moderate (CrCl of 30 to  
521 49 mL/min), and severe (CrCl less than 30 mL/min) renal impairment was compared with  
522 subjects with normal renal function. Average total plasma eltrombopag AUC<sub>0-∞</sub> was 32% to 36%  
523 lower in subjects with mild to moderate renal impairment and 60% lower in subjects with severe  
524 renal impairment compared with healthy subjects. The effect of renal impairment on unbound  
525 (active) eltrombopag exposure has not been assessed.

526 **12.6 Assessment of Risk of QT/QTc Prolongation**

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

533 **13 NONCLINICAL TOXICOLOGY**

534 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

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

549 Eltrombopag did not affect male fertility in rats at doses up to 40 mg/kg/day, the highest dose  
550 tested (3 times the human clinical exposure based on AUC in ITP patients at 75 mg/day and 2  
551 times the human clinical exposure based on AUC in chronic hepatitis C patients at 100 mg/day).

552 **13.2 Animal Pharmacology and/or Toxicology**

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

555 Treatment-related cataracts were detected in rodents in a dose- and time-dependent  
556 manner. At greater than or equal to 6 times the human clinical exposure based on AUC in ITP  
557 patients at 75 mg/day and 3 times the human clinical exposure based on AUC in chronic hepatitis  
558 C patients at 100 mg/day, cataracts were observed in mice after 6 weeks and in rats after  
559 28 weeks of dosing. At greater than or equal to 4 times the human clinical exposure based on  
560 AUC in ITP patients at 75 mg/day and 2 times the human clinical exposure based on AUC in  
561 chronic hepatitis C patients at 100 mg/day, cataracts were observed in mice after 13 weeks and in  
562 rats after 39 weeks of dosing [*see Warnings and Precautions (5.4)*].

563 Renal tubular toxicity was observed in studies up to 14 days in duration in mice and rats  
564 at exposures that were generally associated with morbidity and mortality. Tubular toxicity was

565 also observed in a 2-year oral carcinogenicity study in mice at doses of 25, 75, and  
566 150 mg/kg/day. The exposure at the lowest dose was 1.2 times the human clinical exposure  
567 based on AUC in ITP patients at 75 mg/day and 0.6 times the human clinical exposure based on  
568 AUC in chronic hepatitis C patients at 100 mg/day. No similar effects were observed in mice  
569 after 13 weeks at exposures greater than those associated with renal changes in the 2-year study,  
570 suggesting that this effect is both dose- and time-dependent.

## 571 **14 CLINICAL STUDIES**

### 572 **14.1 Chronic ITP**

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

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

583 The median age of the patients was 50 years and 60% were female. Approximately 70%  
584 of the patients had received at least 2 prior ITP therapies (predominantly corticosteroids,  
585 immunoglobulins, rituximab, cytotoxic therapies, danazol, and azathioprine) and 40% of the  
586 patients had undergone splenectomy. The median baseline platelet counts (approximately  $18 \times$   
587  $10^9/L$ ) were similar among all treatment groups.

588 Trial 1 randomized 114 patients (2:1) to PROMACTA 50 mg or placebo. Trial 2  
589 randomized 117 patients (1:1:1:1) among placebo or 1 of 3 dose regimens of PROMACTA,  
590 30 mg, 50 mg, or 75 mg each administered daily.

591 Table 8 shows for each trial the primary efficacy outcomes for the placebo groups and the  
592 patient groups who received the 50 mg daily regimen of PROMACTA.

593

594 **Table 8. Trials 1 and 2 Platelet Count Response ( $\geq 50 \times 10^9/L$ ) Rates in Adults with Chronic**  
595 **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%)

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

597

598 The platelet count response to PROMACTA was similar among patients who had or had  
599 not undergone splenectomy. In general, increases in platelet counts were detected 1 week

600 following initiation of PROMACTA and the maximum response was observed after 2 weeks of  
601 therapy. In the placebo and 50 mg dose groups of PROMACTA, the trial drug was discontinued  
602 due to an increase in platelet counts to greater than  $200 \times 10^9/L$  in 3% and 27% of the patients,  
603 respectively. The median duration of treatment with the 50 mg dose of PROMACTA was  
604 42 days in Trial 1 and 43 days in Trial 2.

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

609 **Trial 3:** In this trial, 197 patients were randomized (2:1) to receive either PROMACTA  
610 50 mg once daily (n = 135) or placebo (n = 62) for 6 months, during which time the dose of  
611 PROMACTA could be adjusted based on individual platelet counts. Patients were allowed to  
612 taper or discontinue concomitant ITP medications after being treated with PROMACTA for  
613 6 weeks. Patients were permitted to receive rescue treatments at any time during the trial as  
614 clinically indicated. The primary endpoint was the odds of achieving a platelet count greater than  
615 or equal to  $50 \times 10^9/L$  and less than or equal to  $400 \times 10^9/L$  for patients receiving PROMACTA  
616 relative to placebo and was based on patient response profiles throughout the 6-month treatment  
617 period.

618 The median age of the patients treated with PROMACTA and placebo was 47 years and  
619 52.5 years, respectively. Approximately half of the patients treated with PROMACTA and  
620 placebo (47% and 50%, respectively) were receiving concomitant ITP medication  
621 (predominantly corticosteroids) at randomization and had baseline platelet counts less than or  
622 equal to  $15 \times 10^9/L$  (50% and 48%, respectively). A similar percentage of patients treated with  
623 PROMACTA and placebo (37% and 34%, respectively) had a prior splenectomy.

624 In 134 patients who completed 26 weeks of treatment, a sustained platelet response  
625 (platelet count greater than or equal to  $50 \times 10^9/L$  and less than or equal to  $400 \times 10^9/L$  for 6 out  
626 of the last 8 weeks of the 26-week treatment period in the absence of rescue medication at any  
627 time) was achieved by 60% of patients treated with PROMACTA, compared with 10% of  
628 patients treated with placebo (splenectomized patients: PROMACTA 51%, placebo 8%; non-  
629 splenectomized patients: PROMACTA 66%, placebo 11%). The proportion of responders in the  
630 group of patients treated with PROMACTA was between 37% and 56% compared with 7% and  
631 19% in the placebo treatment group for all on-therapy visits. Patients treated with PROMACTA  
632 were significantly more likely to achieve a platelet count between  $50 \times 10^9/L$  and  $400 \times 10^9/L$   
633 during the entire 6-month treatment period compared with those patients treated with placebo.

634 Outcomes of treatment are presented in Table 9 for all patients enrolled in the trial.  
635

636 **Table 9. Outcomes of Treatment from Trial 3 in Adults with Chronic Immune (Idiopathic)**  
637 **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)

638  
639 Among 94 patients receiving other ITP therapy at baseline, 37 (59%) of 63 patients  
640 treated with PROMACTA and 10 (32%) of 31 patients in the placebo group discontinued  
641 concomitant therapy at some time during the trial.

642 **Extension Trial:** Patients who completed any prior clinical trial with PROMACTA were  
643 enrolled in an open-label, single-arm trial in which attempts were made to decrease the dose or  
644 eliminate the need for any concomitant ITP medications. PROMACTA was administered to 299  
645 patients; 249 completed 6 months, 210 patients completed 12 months, and 138 patients  
646 completed 24 months of therapy. The median baseline platelet count was  $19 \times 10^9/L$  prior to  
647 administration of PROMACTA.

#### 648 **14.2 Chronic Hepatitis C-associated Thrombocytopenia**

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

672 phase or to placebo. PROMACTA was administered in combination with pegylated interferon  
673 and ribavirin per their respective prescribing information for up to 48 weeks.

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

679 In both trials, a significantly greater proportion of patients treated with PROMACTA  
680 achieved SVR (see Table 10). The improvement in the proportion of patients who achieved SVR  
681 was consistent across subgroups based on baseline platelet count (less than  $50 \times 10^9/L$  versus  
682 greater than or equal to  $50 \times 10^9/L$ ). In patients with high baseline viral loads (greater than or  
683 equal to 800,000), the SVR rate was 18% (82/452) for PROMACTA versus 8% (20/239) for  
684 placebo.

685

686 **Table 10. 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>	<b>N = 715</b>		<b>N = 805</b>	
% Patients who achieved target platelet counts and initiated antiviral therapy <sup>c</sup>	95%		94%	
<b>Antiviral Treatment Phase</b>	<b>PROMACTA N = 450</b>	<b>Placebo N = 232</b>	<b>PROMACTA N = 506</b>	<b>Placebo N = 253</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

687 <sup>a</sup> PROMACTA given in combination with peginterferon alfa-2a (180 mcg once weekly for  
688 48 weeks for genotypes 1/4/6; 24 weeks for genotype 2 or 3) plus ribavirin (800 to 1,200 mg  
689 daily in 2 divided doses orally).

690 <sup>b</sup> PROMACTA given in combination with peginterferon alfa-2b (1.5 mcg/kg once weekly for  
691 48 weeks for genotypes 1/4/6; 24 weeks for genotype 2 or 3) plus ribavirin (800 to 1,400 mg  
692 daily in 2 divided doses orally).

693 <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.

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

695

696 The majority of patients treated with PROMACTA (76%) maintained a platelet count  
697 greater than or equal to  $50 \times 10^9/L$  compared with 19% for placebo. A greater proportion of  
698 patients on PROMACTA did not require any antiviral dose reduction as compared with placebo  
699 (45% versus 27%).

700 **14.3 Severe Aplastic Anemia**

701 PROMACTA was studied in a single-arm, single-center, open-label trial in 43 patients  
702 with severe aplastic anemia who had an insufficient response to at least one prior  
703 immunosuppressive therapy and who had a platelet count less than or equal to  $30 \times 10^9/L$ .  
704 PROMACTA was administered at an initial dose of 50 mg once daily for 2 weeks and increased  
705 over 2 week periods up to a maximum dose of 150 mg once daily. The primary endpoint was  
706 hematologic response assessed after 12 weeks of treatment with PROMACTA. Hematologic  
707 response was defined as meeting 1 or more of the following criteria: 1) platelet count increases to  
708  $20 \times 10^9/L$  above baseline, or stable platelet counts with transfusion independence for a  
709 minimum of 8 weeks; 2) hemoglobin increase by greater than 1.5g/dL, or a reduction in greater  
710 than or equal to 4 units of RBC transfusions for 8 consecutive weeks; 3) ANC increase of 100%  
711 or an ANC increase greater than  $0.5 \times 10^9/L$ . PROMACTA was discontinued after 16 weeks if  
712 no hematologic response was observed. Patients who responded continued therapy in an  
713 extension phase of the trial.

714 The treated population had median age of 45 years (range 17 to 77 years) and 56% were  
715 male. At baseline, the median platelet count was  $20 \times 10^9/L$ , hemoglobin was 8.4 g/dL, ANC was  
716  $0.58 \times 10^9/L$  and absolute reticulocyte count was  $24.3 \times 10^9/L$ . Eighty-six percent of patients were  
717 RBC transfusion dependent and 91% were platelet transfusion dependent. The majority of  
718 patients (84%) received at least 2 prior immunosuppressive therapies. Three patients had  
719 cytogenetic abnormalities at baseline.

720 Table 11 presents the primary efficacy results.

721

722 **Table 11. Hematologic Response in Patients with Severe Aplastic Anemia**

Outcome	PROMACTA N = 43
Response Rate <sup>a</sup> , n (%)	17 (40)
95% CI (%)	(25, 56)
Median of Duration of Response in Months (95% CI)	NR <sup>b</sup> (3.0, NR <sup>b</sup> )

723 <sup>a</sup> Includes single and multi-lineage.

724 <sup>b</sup> NR = not reached due to few events (relapsed).

725

726 In the 17 responders, the platelet transfusion-free period ranged from 8 to 1,096 days with  
727 a median of 200 days, and the RBC transfusion-free period ranged from 15 to 1,082 days with a  
728 median of 208 days.

729 In the extension phase, 8 patients achieved a multi-lineage response; 4 of these patients  
730 subsequently tapered off treatment with PROMACTA and maintained the response (median  
731 follow up 8.1 months, range 7.2-10.6 months).

732

733

734

735 **16 HOW SUPPLIED/STORAGE AND HANDLING**

- 736 • The 12.5 mg tablets are round, biconvex, white, film-coated tablets debossed with GS MZ1  
737 and 12.5 on one side and are available in bottles of 30: NDC 0007-4643-13.
- 738 • The 25 mg tablets are round, biconvex, orange, film-coated tablets debossed with GS NX3  
739 and 25 on one side and are available in bottles of 30: NDC 0007-4640-13.
- 740 • The 50 mg tablets are round, biconvex, blue, film-coated tablets debossed with GS UFU and  
741 50 on one side and are available in bottles of 30: NDC 0007-4641-13.
- 742 • The 75 mg tablets are round, biconvex, pink, film-coated tablets debossed with GS FFS and  
743 75 on one side and are available in bottles of 30: NDC 0007-4642-13.
- 744 • The 100 mg tablets are round, biconvex, green, film-coated tablets debossed with GS 1L5  
745 and are available in bottles of 30: NDC 0007-4646-13. This product contains a desiccant.

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

749 **17 PATIENT COUNSELING INFORMATION**

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

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

- 753 • For patients with chronic ITP, therapy with PROMACTA is administered to achieve and  
754 maintain a platelet count greater than or equal to  $50 \times 10^9/L$  as necessary to reduce the risk  
755 for bleeding.
- 756 • For patients with chronic hepatitis C, therapy with PROMACTA is administered to achieve  
757 and maintain a platelet count necessary to initiate and maintain antiviral therapy with  
758 pegylated interferon and ribavirin.
- 759 • Therapy with PROMACTA may be associated with hepatobiliary laboratory abnormalities.
- 760 • Advise patients with chronic hepatitis C and cirrhosis that they may be at risk for hepatic  
761 decompensation when receiving alfa interferon therapy.
- 762 • Advise patients that they should report any of the following signs and symptoms of liver  
763 problems to their healthcare provider right away.
- 764 • yellowing of the skin or the whites of the eyes (jaundice)
- 765 • unusual darkening of the urine
- 766 • unusual tiredness
- 767 • right upper stomach area pain
- 768 • confusion
- 769 • swelling of the stomach area (abdomen)
- 770 • Advise patients that thrombocytopenia and risk of bleeding may reoccur upon discontinuing  
771 PROMACTA, particularly if PROMACTA is discontinued while the patient is on  
772 anticoagulants or antiplatelet agents.

- 773 • Advise patients that too much PROMACTA may result in excessive platelet counts and a risk  
774 for thrombotic/thromboembolic complications.
- 775 • Advise patients that during therapy with PROMACTA, they should continue to avoid  
776 situations or medications that may increase the risk for bleeding.
- 777 • Advise patients to have a baseline ocular examination prior to administration of  
778 PROMACTA and be monitored for signs and symptoms of cataracts during therapy.
- 779 • Advise patients to keep at least a 4-hour interval between PROMACTA and foods, mineral  
780 supplements, and antacids which contain polyvalent cations such as iron, calcium, aluminum,  
781 magnesium, selenium, and zinc.

782

783 PROMACTA is a registered trademark of the GSK group of companies. The following are  
784 registered trademarks of their respective owners: PEGASYS/Hoffmann-La Roche Inc.;  
785 PEGINTRON/Schering Corporation.

786



787

788 GlaxoSmithKline

789 Research Triangle Park, NC 27709

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## MEDICATION GUIDE

### PROMACTA<sup>®</sup> (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.** If you have chronic hepatitis C virus, and take PROMACTA with interferon and ribavirin treatment, PROMACTA may increase your risk of liver problems. 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)

**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 people with:

- low blood platelet counts due to chronic immune (idiopathic) thrombocytopenia (ITP), when other medicines to treat your ITP or surgery to remove the spleen have not worked well enough
- low blood platelet counts due to chronic hepatitis C virus (HCV) infection before and during treatment with interferon
- severe aplastic anemia (SAA) when other medicines to treat your SAA have not worked well enough

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

837

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

839

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

843

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

846

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

848

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

850

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

- 852 • have liver or kidney problems
- 853 • have or had a blood clot
- 854 • have a history of cataracts
- 855 • have had surgery to remove your spleen (splenectomy)
- 856 • have bleeding problems
- 857 • are Asian and you are of Chinese, Japanese, Taiwanese, or Korean ancestry. You  
858 may need a lower dose of PROMACTA.
- 859 • have any other medical conditions
- 860 • are pregnant or plan to become pregnant. It is not known if PROMACTA will  
861 harm an unborn baby.
- 862 • are breastfeeding or plan to breastfeed. It is not known if PROMACTA passes  
863 into your breast milk. You and your healthcare provider should decide whether  
864 you will take PROMACTA or breastfeed. You should not do both.

865

866 **Tell your healthcare provider about all the medicines you take**, including  
867 prescription and over-the-counter medicines, vitamins, and herbal supplements.  
868 PROMACTA may affect the way certain medicines work. Certain other medicines  
869 may affect the way PROMACTA works.

870

871 Especially tell your healthcare provider if you take:

- 872 • certain medicines used to treat high cholesterol, called “statins”
- 873 • a blood thinner medicine

874

875 Certain medicines may keep PROMACTA from working correctly. Take PROMACTA at  
876 least 4 hours before or 4 hours after taking these products:

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

880

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

883

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

886

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

888

- 889 • Take PROMACTA exactly as your healthcare provider tells you to take it. Do not  
890 stop taking PROMACTA without talking with your healthcare provider first. Do  
891 not change your dose or schedule for taking PROMACTA unless your healthcare  
892 provider tells you to change it.
- 893 • Take PROMACTA on an empty stomach, either 1 hour before or 2 hours after  
894 eating food.
- 895 • Take PROMACTA at least 4 hours before or 4 hours after eating dairy products  
896 and calcium fortified juices.
- 897 • If you miss a dose of PROMACTA, wait and take your next scheduled dose. Do  
898 not take more than one dose of PROMACTA in one day.
- 899 • If you take too much PROMACTA, you may have a higher risk of serious side  
900 effects. Call your healthcare provider right away.
- 901 • Your healthcare provider will check your platelet count during your treatment  
902 with PROMACTA and change your dose of PROMACTA as needed.
- 903 • Tell your healthcare provider about any bruising or bleeding that happens while  
904 you take and after you stop taking PROMACTA.

905

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

907

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

909

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

911

912 PROMACTA may cause serious side effects, including:

913

- 914 • See **“What is the most important information I should know about**  
915 **PROMACTA?”**
- 916 • **Abnormal liver function tests.** Your healthcare provider will order blood tests  
917 to check your liver before you start taking PROMACTA and during your  
918 treatment. In some cases treatment with PROMACTA may need to be stopped  
919 due to changes in your liver function tests.
- 920 • **High platelet counts and higher risk for blood clots.** Your risk of getting a  
921 blood clot is increased if your platelet count is too high during treatment with  
922 PROMACTA. Your risk of getting a blood clot may also be increased during  
923 treatment with PROMACTA if you have normal or low platelet counts. You may  
924 have severe problems or die from some forms of blood clots, such as clots that  
925 travel to the lungs or that cause heart attacks or strokes. Your healthcare  
926 provider will check your blood platelet counts, and change your dose or stop  
927 PROMACTA if your platelet counts get too high. Tell your healthcare provider  
928 right away if you have signs and symptoms of a blood clot in the leg, such as  
929 swelling, pain, or tenderness in your leg.
- 930 People with chronic liver disease may be at risk for a type of blood clot in the  
931 stomach area. Tell your healthcare provider right away if you have stomach area  
932 pain that may be a symptom of this type of blood clot.
- 933 • **New or worsened cataracts (a clouding of the lens in the eye).** New or  
934 worsened cataracts have happened in people taking PROMACTA. Your healthcare  
935 provider will check your eyes before and during your treatment with PROMACTA.  
936 Tell your healthcare provider about any changes in your eyesight while taking  
937 PROMACTA.

938

939 **The most common side effects of PROMACTA when used to treat chronic**  
940 **ITP are:**

- 941 • nausea
- 942 • diarrhea
- 943 • upper respiratory tract infection. Symptoms may include runny nose, stuffy  
944 nose, and sneezing
- 945 • vomiting
- 946 • muscle aches
- 947 • urinary tract infection. Symptoms may include frequent or urgent need to  
948 urinate, low fever in some people, pain or burning with urination.
- 949 • pain or swelling (inflammation) in your throat or mouth (oropharyngeal pain and  
950 pharyngitis)
- 951 • abnormal liver function tests
- 952 • back pain
- 953 • “flu” like symptoms (influenza) including fever, headache, tiredness, cough, sore

- 954 throat, and body aches
- 955 • skin tingling, itching, or burning
- 956 • rash

957

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

- 960 • low red blood cell count (anemia)
- 961 • fever
- 962 • tiredness
- 963 • headache
- 964 • nausea
- 965 • diarrhea
- 966 • decreased appetite
- 967 • “flu” like symptoms (influenza) including fever, headache, tiredness, cough, sore
- 968 throat, and body aches
- 969 • feeling weak
- 970 • trouble sleeping
- 971 • cough
- 972 • itching
- 973 • chills
- 974 • muscle aches
- 975 • hair loss
- 976 • swelling in your ankles, feet, and legs

977

978 **The most common side effects when PROMACTA is used to treat severe**  
979 **aplastic anemia are:**

- 980 • nausea
- 981 • feeling tired
- 982 • cough
- 983 • diarrhea
- 984 • headache
- 985 • pain in arms, legs, hands or feet
- 986 • shortness of breath
- 987 • fever
- 988 • dizziness
- 989 • pain in the nose or throat
- 990 • abdominal pain
- 991 • bruising
- 992 • muscle spasms
- 993 • abnormal liver function tests

- 994 • joint pain
- 995 • runny nose

996

997 Laboratory tests may show abnormal changes to the cells in your bone marrow.

998

999 Tell your healthcare provider if you have any side effect that bothers you or that  
1000 does not go away.

1001

1002 These are not all the possible side effects of PROMACTA. For more information, ask  
1003 your healthcare provider or pharmacist.

1004

1005 Call your doctor for medical advice about side effects. You may report side effects  
1006 to FDA at 1-800-FDA-1088.

1007

#### 1008 **How should I store PROMACTA tablets?**

1009

- 1010 • Store PROMACTA at room temperature between 68°F to 77°F (20°C to 25°C).
- 1011 • Keep PROMACTA tightly closed in the bottle given to you.
- 1012 • The PROMACTA bottle may contain a desiccant pack to help keep your medicine  
1013 dry. Do not remove the desiccant pack from the bottle.

#### 1014 **Keep PROMACTA and all medicines out of the reach of children.**

1015

#### 1016 **General information about the safe and effective use of PROMACTA**

1017

1018 Medicines are sometimes prescribed for purposes other than those listed in a  
1019 Medication Guide. Do not use PROMACTA for a condition for which it was not  
1020 prescribed. Do not give PROMACTA to other people, even if they have the same  
1021 symptoms that you have. It may harm them.

1022

1023 This Medication Guide summarizes the most important information about  
1024 PROMACTA. If you would like more information, talk with your healthcare provider.  
1025 You can ask your healthcare provider or pharmacist for information about  
1026 PROMACTA that is written for health professionals.

1027

1028 For more information about PROMACTA, go to [www.PROMACTA.com](http://www.PROMACTA.com) or call 1-888-  
1029 825-5249.

1030

1031 **What are the ingredients in PROMACTA?**

1032

1033 **Active ingredient:** eltrombopag olamine.

1034 **Inactive ingredients:**

- 1035 • **Tablet Core:** magnesium stearate, mannitol, microcrystalline cellulose,  
1036 povidone, and sodium starch glycolate.
- 1037 • **Coating:** hypromellose (12.5 mg, 25 mg, 50 mg, and 75 mg tablets) or  
1038 polyvinyl alcohol and talc (100 mg tablet), polyethylene glycol 400, titanium  
1039 dioxide, polysorbate 80 (12.5 mg tablet), and FD&C Yellow No. 6 aluminum lake  
1040 (25 mg tablet), FD&C Blue No. 2 aluminum lake (50 mg tablet), Iron Oxide Red  
1041 and Iron Oxide Black (75 mg tablet), or Iron Oxide Yellow and Iron Oxide Black  
1042 (100 mg tablet).

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1044 **This Medication Guide has been approved by the U.S. Food and Drug**  
1045 **Administration.**

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1049 GlaxoSmithKline

1050 Research Triangle Park, NC 27709

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