

## 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 (1.3)	04/2014
Warnings and Precautions, Hepatic Decompensation in Patients With Chronic Hepatitis C moved (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)

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 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-based therapy or limits the ability to maintain interferon-based therapy. (1.3)
- Safety and efficacy have not been established in combination with direct-acting antiviral agents used without interferon for treatment of chronic hepatitis C infection. (1.3)

### DOSAGE AND ADMINISTRATION

- Take on an empty stomach (1 hour before or 2 hours after a meal). (2.3)
- 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). (2.3)

- **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

- 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 ( $\geq 3\%$  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. (6.1)

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: 04/2014

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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 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 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).

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

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

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

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

49

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

<b>Platelet Count Result</b>	<b>Dose Adjustment or Response</b>
< $50 \times 10^9/L$ 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.

52

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

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

58 **Discontinuation:** Discontinue PROMACTA if the platelet count does not increase to a  
59 level sufficient to avoid clinically important bleeding after 4 weeks of therapy with  
60 PROMACTA at the maximum daily dose of 75 mg. Excessive platelet count responses, as

61 outlined in Table 1, or important liver test abnormalities also necessitate discontinuation of  
62 PROMACTA [see *Warnings and Precautions (5.2)*]. Obtain CBCs with differentials, including  
63 platelet counts, weekly for at least 4 weeks following discontinuation of PROMACTA.

64 **2.2 Chronic Hepatitis C-Associated Thrombocytopenia**

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

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

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

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

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

81  
82

**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, 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.

83  
84  
85

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

86 pegylated interferon and ribavirin prescribing information for discontinuation recommendations  
87 for antiviral treatment futility.

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

### 91 **2.3 Administration**

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

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

## 98 **3 DOSAGE FORMS AND STRENGTHS**

- 99 • 12.5 mg tablets — round, biconvex, white, film-coated tablets debossed with GS MZ1 and  
100 12.5 on one side. Each tablet, for oral administration, contains eltrombopag olamine,  
101 equivalent to 12.5 mg of eltrombopag free acid.
- 102 • 25 mg tablets — round, biconvex, orange, film-coated tablets debossed with GS NX3 and  
103 25 on one side. Each tablet, for oral administration, contains eltrombopag olamine,  
104 equivalent to 25 mg of eltrombopag free acid.
- 105 • 50 mg tablets — round, biconvex, blue, film-coated tablets debossed with GS UFU and 50 on  
106 one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to  
107 50 mg of eltrombopag free acid.
- 108 • 75 mg tablets — round, biconvex, pink, film-coated tablets debossed with GS FFS and 75 on  
109 one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to  
110 75 mg of eltrombopag free acid.
- 111 • 100 mg tablets — round, biconvex, green, film-coated tablets debossed with GS 1L5. Each  
112 tablet, for oral administration, contains eltrombopag olamine, equivalent to 100 mg of  
113 eltrombopag free acid.

## 114 **4 CONTRAINDICATIONS**

115 None.

## 116 **5 WARNINGS AND PRECAUTIONS**

### 117 **5.1 Hepatic Decompensation in Patients With Chronic Hepatitis C**

118 In patients with chronic hepatitis C, PROMACTA in combination with interferon and  
119 ribavirin may increase the risk of hepatic decompensation. In two controlled clinical trials in  
120 patients with chronic hepatitis C and thrombocytopenia, ascites and encephalopathy occurred  
121 more frequently on the arm receiving PROMACTA plus antivirals treatment (7%) than the  
122 placebo plus antivirals arm (4%). Patients with low albumin levels (<3.5 g/dL) or Model for  
123 End-Stage Liver Disease (MELD) score  $\geq 10$  at baseline had a greater risk for hepatic

124 | decompensation on the arm receiving PROMACTA plus antivirals treatment. Discontinue  
125 | PROMACTA if antiviral therapy is discontinued.

## 126 | **5.2 Hepatotoxicity**

127 | PROMACTA can cause liver enzyme elevations [*see Adverse Reactions (6.1)*]. Measure  
128 | serum ALT, AST, and bilirubin prior to initiation of PROMACTA, every 2 weeks during the  
129 | dose adjustment phase, and monthly following establishment of a stable dose. PROMACTA  
130 | inhibits UGT1A1 and OATP1B1, which may lead to indirect hyperbilirubinemia. If bilirubin is  
131 | elevated, perform fractionation. Evaluate abnormal serum liver tests with repeat testing within 3  
132 | to 5 days. If the abnormalities are confirmed, monitor serum liver tests weekly until resolved or  
133 | stabilized. Discontinue PROMACTA if ALT levels increase to  $\geq 3X$  ULN in patients with normal  
134 | liver function or  $\geq 3X$  baseline in patients with pre-treatment elevations in transaminases and are:

- 135 | • progressively increasing, or
- 136 | • persistent for  $\geq 4$  weeks, or
- 137 | • accompanied by increased direct bilirubin, or
- 138 | • accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation.

139 | If the potential benefit for reinitiating treatment with PROMACTA is considered to  
140 | outweigh the risk for hepatotoxicity, then consider cautiously reintroducing PROMACTA and  
141 | measure serum liver tests weekly during the dose adjustment phase. Hepatotoxicity may reoccur  
142 | if PROMACTA is reinitiated. If liver tests abnormalities persist, worsen or recur, then  
143 | permanently discontinue PROMACTA.

## 144 | **5.3 Thrombotic/Thromboembolic Complications**

145 | In 2 controlled clinical trials in patients with chronic hepatitis C and thrombocytopenia,  
146 | 3% (31/955) treated with PROMACTA experienced a thrombotic event compared to 1% (5/484)  
147 | on placebo. The majority of events were of the portal venous system (1% in patients treated with  
148 | PROMACTA versus  $< 1\%$  for placebo).

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

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

158 | In a controlled trial in non-ITP thrombocytopenic patients with chronic liver disease  
159 | undergoing elective invasive procedures (N = 292), the risk of thrombotic events was increased  
160 | in patients treated with 75 mg PROMACTA once daily. Seven thrombotic complications (six  
161 | patients) were reported in the group that received PROMACTA and three thrombotic  
162 | complications were reported in the placebo group (two patients). All of the thrombotic  
163 | complications reported in the group that received PROMACTA were portal vein thrombosis

164 (PVT). Symptoms of PVT included abdominal pain, nausea, vomiting, and diarrhea. Five of the  
165 six patients in the group that received PROMACTA experienced a thrombotic complication  
166 within 30 days of completing treatment with PROMACTA and at a platelet count above  $200 \times$   
167  $10^9/L$ . The risk of portal venous thrombosis was increased in thrombocytopenic patients with  
168 chronic liver disease treated with 75 mg PROMACTA once daily for 2 weeks in preparation for  
169 invasive procedures.

#### 170 **5.4 Cataracts**

171 In the 3 controlled clinical trials in chronic ITP, cataracts developed or worsened in 15  
172 (7%) patients who received 50 mg PROMACTA daily and 8 (7%) placebo-group patients. In the  
173 extension trial, cataracts developed or worsened in 4% of patients who underwent ocular  
174 examination prior to therapy with PROMACTA. In the 2 controlled clinical trials in patients with  
175 chronic hepatitis C and thrombocytopenia, cataracts developed or worsened in 8% patients  
176 treated with PROMACTA and 5% patients treated with placebo.

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

### 181 **6 ADVERSE REACTIONS**

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

- 184 • Hepatic Decompensation in Patients With Chronic Hepatitis C [*see Warnings and*  
185 *Precautions (5.1)*]
- 186 • Hepatotoxicity [*see Warnings and Precautions (5.2)*]
- 187 • Thrombotic/Thromboembolic Complications [*see Warnings and Precautions (5.3)*]
- 188 • Cataracts [*see Warnings and Precautions (5.4)*]

#### 189 **6.1 Clinical Trials Experience**

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

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

197 The data described below reflect exposure of PROMACTA to 446 patients with chronic  
198 ITP aged 18 to 85, of whom 65% were female across the ITP clinical development program  
199 including 3 placebo-controlled trials. PROMACTA was administered to 277 patients for at least  
200 6 months and 202 patients for at least 1 year.

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

204

205 **Table 3. Adverse Reactions ( $\geq 3\%$ ) from Three Placebo-Controlled Trials in Adults With**  
206 **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

207

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

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

215

216 **Table 4. Treatment-Related Adverse Reactions ( $\geq 3\%$ ) from Extension Trial in Adults With**  
217 **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

218

219 In the 3 controlled chronic ITP trials, serum liver test abnormalities (predominantly  
220 Grade 2 or less in severity) were reported in 11% and 7% of the PROMACTA and placebo  
221 groups, respectively. Four patients (1%) treated with PROMACTA and three patients in the  
222 placebo group (2%) discontinued treatment due to hepatobiliary laboratory abnormalities. Seven  
223 of the patients treated with PROMACTA in the controlled trials with hepatobiliary laboratory  
224 abnormalities were re-exposed to PROMACTA in the extension trial. Six of these patients again  
225 experienced liver test abnormalities (predominantly Grade 1) resulting in discontinuation of  
226 PROMACTA in one patient. In the extension chronic ITP trial, one additional patient had  
227 PROMACTA discontinued due to liver test abnormalities ( $\leq$ Grade 3).

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

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

235

236 **Table 5. Adverse Reactions ( $\geq 10\%$  and Greater than Placebo) from Two Placebo-**  
237 **Controlled Trials in Adults With Chronic Hepatitis C**

<b>Adverse Reaction</b>	<b>PROMACTA + Peginterferon/Ribavirin n = 955 (%)</b>	<b>Placebo + Peginterferon/Ribavirin n = 484 (%)</b>
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

238  
239 In the 2 controlled clinical trials in patients with chronic hepatitis C, hyperbilirubinemia  
240 was reported in 8% of patients receiving PROMACTA compared to 3% for placebo. Total  
241 bilirubin  $\geq 1.5$  X ULN was reported in 76% and 50% of patients receiving PROMACTA and  
242 placebo, respectively. ALT or AST  $\geq 3$ X ULN was reported in 34% and 38% of the  
243 PROMACTA and placebo groups, respectively.

244 **7 DRUG INTERACTIONS**

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

250 **7.1 Polyvalent Cations (Chelation)**

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

255 PROMACTA must not be taken within 4 hours of any medications or products  
256 containing polyvalent cations such as antacids, dairy products, and mineral supplements to avoid  
257 significant reduction in PROMACTA absorption due to chelation [see *Dosage and*  
258 *Administration (2.3)*].

## 259 **7.2 Transporters**

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

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

## 271 **7.3 Protease Inhibitors**

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

277 Hepatitis C Virus (HCV) Protease Inhibitors: Coadministration of PROMACTA with  
278 either boceprevir or telaprevir did not affect eltrombopag or protease inhibitor exposure  
279 significantly [see *Clinical Pharmacology (12.3)*]. No dose adjustments are recommended. Drug  
280 interactions with other HCV protease inhibitors have not been evaluated.

## 281 **7.4 Peginterferon Alfa 2a/b Therapy**

282 Co-administration of peginterferon alfa 2a (PEGASYS<sup>®</sup>) or 2b (PEGINTRON<sup>®</sup>) did not  
283 affect eltrombopag exposure in 2 randomized, double-blind, placebo-controlled trials with adult  
284 patients with chronic hepatitis C [see *Clinical Pharmacology (12.3)*].

# 285 **8 USE IN SPECIFIC POPULATIONS**

## 286 **8.1 Pregnancy**

287 Pregnancy Category C

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

292 **Pregnancy Registry:** A pregnancy registry has been established to collect information  
293 about the effects of PROMACTA during pregnancy. Physicians are encouraged to register

294 pregnant patients, or pregnant women may enroll themselves in the PROMACTA pregnancy  
295 registry by calling 1-888-825-5249.

296 In an early embryonic development study, female rats received oral eltrombopag at doses  
297 of 10, 20, or 60 mg/kg/day (0.8, 2, and 6 times, respectively, the human clinical exposure based  
298 on AUC in ITP patients at 75 mg/day and 0.3, 1, and 3 times, respectively, the human clinical  
299 exposure based on AUC in chronic hepatitis C patients at 100 mg/day). Increased pre- and post-  
300 implantation loss and reduced fetal weight were observed at the highest dose which also caused  
301 maternal toxicity.

302 Eltrombopag was administered orally to pregnant rats at 10, 20, or 60 mg/kg/day (0.8, 2,  
303 and 6 times, respectively, the human clinical exposure based on AUC in ITP patients at  
304 75 mg/day and 0.3, 1, and 3 times, respectively, the human clinical exposure based on AUC in  
305 chronic hepatitis C patients at 100 mg/day). Decreased fetal weights (6% to 7%) and a slight  
306 increase in the presence of cervical ribs were observed at the highest dose which also caused  
307 maternal toxicity. However, no evidence of major structural malformations was observed.

308 Pregnant rabbits were treated with oral eltrombopag doses of 30, 80, or 150 mg/kg/day  
309 (0.04, 0.3, and 0.5 times, respectively, the human clinical exposure based on AUC in ITP  
310 patients at 75 mg/day and 0.02, 0.1, and 0.3 times, respectively, the human clinical exposure  
311 based on AUC in chronic hepatitis C patients at 100 mg/day). No evidence of fetotoxicity,  
312 embryolethality, or teratogenicity was observed.

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

### 320 **8.3 Nursing Mothers**

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

### 325 **8.4 Pediatric Use**

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

### 327 **8.5 Geriatric Use**

328 Of the 106 patients in 2 randomized clinical trials of PROMACTA 50 mg in chronic ITP,  
329 22% were 65 years of age and over, while 9% were 75 years of age and over. In the 2  
330 randomized clinical trials of PROMACTA in patients with chronic hepatitis C and  
331 thrombocytopenia, 7% were 65 years of age and over, while fewer than 1% were 75 years of age  
332 and over. No overall differences in safety or effectiveness were observed between these patients

333 and younger patients in the placebo-controlled trials, but greater sensitivity of some older  
334 individuals cannot be ruled out.

## 335 **8.6 Hepatic Impairment**

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

338 A reduction in the initial dose of PROMACTA in patients with chronic ITP is  
339 recommended for patients with hepatic impairment (Child-Pugh Class A, B, C) [*see Dosage and*  
340 *Administration (2.1) and Warnings and Precautions (5.2)*]. No dosage adjustment is necessary  
341 for HCV patients with hepatic impairment [*see Clinical Pharmacology (12.3)*].

## 342 **8.7 Renal Impairment**

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

## 346 **8.8 Ethnicity**

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

## 353 **10 OVERDOSAGE**

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

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

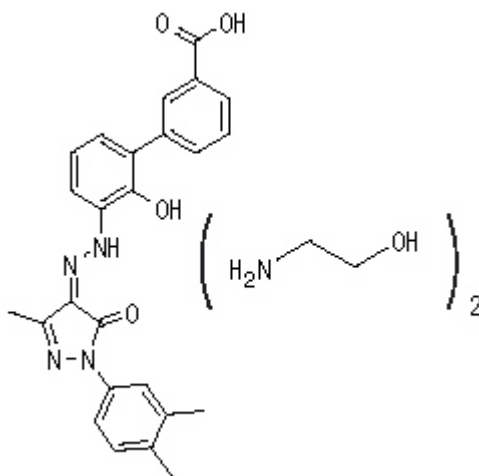
363 In case of an overdose, consider oral administration of a metal cation-containing  
364 preparation, such as calcium, aluminum, or magnesium preparations to chelate eltrombopag and  
365 thus limit absorption. Closely monitor platelet counts. Reinitiate treatment with PROMACTA in  
366 accordance with dosing and administration recommendations [*see Dosage and Administration*  
367 *(2.1, 2.2)*].

## 368 **11 DESCRIPTION**

369 PROMACTA (eltrombopag) tablets contain eltrombopag olamine, a small molecule  
370 thrombopoietin (TPO) receptor agonist for oral administration. Eltrombopag interacts with the  
371 transmembrane domain of the TPO receptor (also known as cMpl) leading to increased platelet

372 production. Each tablet contains eltrombopag olamine in the amount equivalent to 12.5 mg,  
373 25 mg, 50 mg, 75 mg, or 100 mg of eltrombopag free acid.

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



380 Eltrombopag olamine is practically insoluble in aqueous buffer across a pH range of 1 to  
381 7.4, and is sparingly soluble in water.

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

## 390 12 CLINICAL PHARMACOLOGY

### 391 12.1 Mechanism of Action

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

### 395 12.3 Pharmacokinetics

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

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

404 **Distribution:** The concentration of eltrombopag in blood cells is approximately 50% to  
405 79% of plasma concentrations based on a radiolabel study. *In vitro* studies suggest that  
406 eltrombopag is highly bound to human plasma proteins (>99%). Eltrombopag is a substrate of  
407 BCRP, but is not a substrate for P-glycoprotein (P-gp) or OATP1B1.

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

413 **Elimination:** The predominant route of eltrombopag excretion is via feces (59%), and  
414 31% of the dose is found in the urine. Unchanged eltrombopag in feces accounts for  
415 approximately 20% of the dose; unchanged eltrombopag is not detectable in urine. The plasma  
416 elimination half-life of eltrombopag is approximately 21 to 32 hours in healthy subjects and 26  
417 to 35 hours in ITP patients.

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

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

428 **Rosuvastatin:** In a clinical trial, co-administration of 75 mg of PROMACTA once  
429 daily for 5 days with a single 10 mg dose of the OATP1B1 and BCRP substrate, rosuvastatin to  
430 39 healthy adult subjects increased plasma rosuvastatin  $AUC_{0-\infty}$  by 55% and  $C_{max}$  by 103%.

431 **Protease Inhibitors: HIV Protease Inhibitors:** In a clinical trial, co-administration  
432 of repeat dose lopinavir 400 mg/ritonavir 100 mg twice daily with a single dose of PROMACTA  
433 100 mg to 40 healthy adult subjects decreased plasma eltrombopag  $AUC_{0-\infty}$  by 17%.

434 **HCV Protease Inhibitors:** In a clinical trial, co-administration of repeat dose  
435 telaprevir 750 mg every 8 hours or boceprevir 800 mg every 8 hours with a single dose of  
436 PROMACTA 200 mg to healthy adult subjects did not alter plasma telaprevir, boceprevir, or  
437 eltrombopag  $AUC_{0-\infty}$  or  $C_{max}$  to a significant extent.

438 **Pegylated Interferon alfa-2a + Ribavirin and Pegylated Interferon alfa-2b +**  
439 **Ribavirin:** The pharmacokinetics of eltrombopag in both the presence and absence of pegylated

440 interferon alfa 2a and 2b therapy were evaluated using a population pharmacokinetic analysis in  
441 635 patients with chronic hepatitis C. The population PK model estimates of clearance indicate  
442 no significant difference in eltrombopag clearance in the presence of pegylated interferon alfa  
443 plus ribavirin therapy.

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

448 Specific Populations: *Ethnicity:* Based on two population PK analyses of eltrombopag  
449 concentrations in ITP and chronic hepatitis C patients, East Asian (i.e., Japanese, Chinese,  
450 Taiwanese, and Korean) subjects exhibited 50 to 55% higher eltrombopag plasma concentrations  
451 compared to non-East Asian subjects [*see Dosage and Administration (2.1, 2.2)*].

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

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

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

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

477 *Renal Impairment:* The disposition of a single 50 mg dose of PROMACTA in  
478 patients with mild (creatinine clearance (CrCl) of 50 to 80 mL/min), moderate (CrCl of 30 to  
479 49 mL/min), and severe (CrCl less than 30 mL/min) renal impairment was compared to subjects

480 with normal renal function. Average total plasma eltrombopag  $AUC_{0-\infty}$  was 32% to 36% lower  
481 in subjects with mild to moderate renal impairment and 60% lower in subjects with severe renal  
482 impairment compared with healthy subjects. The effect of renal impairment on unbound (active)  
483 eltrombopag exposure has not been assessed.

#### 484 **12.6 Assessment of Risk of QT/QTc Prolongation**

485 There is no indication of a QT/QTc prolonging effect of PROMACTA at doses up to  
486 150 mg daily for 5 days. The effects of PROMACTA at doses up to 150 mg daily for 5 days  
487 (supratherapeutic doses) on the QT/QTc interval was evaluated in a double-blind, randomized,  
488 placebo- and positive-controlled (moxifloxacin 400 mg, single oral dose) crossover trial in  
489 healthy adult subjects. Assay sensitivity was confirmed by significant QTc prolongation by  
490 moxifloxacin.

### 491 **13 NONCLINICAL TOXICOLOGY**

#### 492 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

499 Eltrombopag was not mutagenic or clastogenic in a bacterial mutation assay or in 2 *in*  
500 *vivo* assays in rats (micronucleus and unscheduled DNA synthesis, 10 times the human clinical  
501 exposure based on  $C_{max}$  in ITP patients at 75 mg/day and 7 times the human clinical exposure  
502 based on  $C_{max}$  in chronic hepatitis C patients at 100 mg/day). In the *in vitro* mouse lymphoma  
503 assay, eltrombopag was marginally positive (<3-fold increase in mutation frequency).

504 Eltrombopag did not affect female fertility in rats at doses up to 20 mg/kg/day (2 times  
505 the human clinical exposure based on AUC in ITP patients at 75 mg/day and similar to the  
506 human clinical exposure based on AUC in chronic hepatitis C patients at 100 mg/day).  
507 Eltrombopag did not affect male fertility in rats at doses up to 40 mg/kg/day, the highest dose  
508 tested (3 times the human clinical exposure based on AUC in ITP patients at 75 mg/day and 2  
509 times the human clinical exposure based on AUC in chronic hepatitis C patients at 100 mg/day).

#### 510 **13.2 Animal Pharmacology/Toxicology**

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

513 Treatment-related cataracts were detected in rodents in a dose- and time-dependent  
514 manner. At  $\geq 6$  times the human clinical exposure based on AUC in ITP patients at 75 mg/day  
515 and 3 times the human clinical exposure based on AUC in chronic hepatitis C patients at  
516 100 mg/day, cataracts were observed in mice after 6 weeks and in rats after 28 weeks of dosing.  
517 At  $\geq 4$  times the human clinical exposure based on AUC in ITP patients at 75 mg/day and 2 times  
518 the human clinical exposure based on AUC in chronic hepatitis C patients at 100 mg/day,

519 cataracts were observed in mice after 13 weeks and in rats after 39 weeks of dosing [see  
520 *Warnings and Precautions (5.4)*].

521 Renal tubular toxicity was observed in studies up to 14 days in duration in mice and rats  
522 at exposures that were generally associated with morbidity and mortality. Tubular toxicity was  
523 also observed in a 2-year oral carcinogenicity study in mice at doses of 25, 75, and  
524 150 mg/kg/day. The exposure at the lowest dose was 1.2 times the human clinical exposure  
525 based on AUC in ITP patients at 75 mg/day and 0.6 times the human clinical exposure based on  
526 AUC in chronic hepatitis C patients at 100 mg/day. No similar effects were observed in mice  
527 after 13 weeks at exposures greater than those associated with renal changes in the 2-year study,  
528 suggesting that this effect is both dose- and time-dependent.

## 529 **14 CLINICAL STUDIES**

### 530 **14.1 Chronic ITP**

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

534 Trials 1 and 2: In trials 1 and 2, patients who had completed at least one prior ITP  
535 therapy and who had a platelet count  $<30 \times 10^9/L$  were randomized to receive either  
536 PROMACTA or placebo daily for up to 6 weeks, followed by 6 weeks off therapy. During the  
537 trials, PROMACTA or placebo was discontinued if the platelet count exceeded  $200 \times 10^9/L$ . The  
538 primary efficacy endpoint was response rate, defined as a shift from a baseline platelet count of  
539  $<30 \times 10^9/L$  to  $\geq 50 \times 10^9/L$  at any time during the treatment period.

540 The median age of the patients was 50 years and 60% were female. Approximately 70%  
541 of the patients had received at least 2 prior ITP therapies (predominantly corticosteroids,  
542 immunoglobulins, rituximab, cytotoxic therapies, danazol, and azathioprine) and 40% of the  
543 patients had undergone splenectomy. The median baseline platelet counts (approximately  $18 \times$   
544  $10^9/L$ ) were similar among all treatment groups.

545 Trial 1 randomized 114 patients (2:1) to PROMACTA 50 mg or placebo. Trial 2  
546 randomized 117 patients (1:1:1:1) among placebo or 1 of 3 dose regimens of PROMACTA,  
547 30 mg, 50 mg, or 75 mg each administered daily.

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

550

551 **Table 6. Trials 1 and 2 Platelet Count Response ( $\geq 50 \times 10^9/L$ ) Rates in Adults With Chronic**  
552 **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%)

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

554

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

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

566 **Trial 3:** In this trial, 197 patients were randomized (2:1) to receive either PROMACTA  
567 50 mg once daily ( $n = 135$ ) or placebo ( $n = 62$ ) for 6 months, during which time the dose of  
568 PROMACTA could be adjusted based on individual platelet counts. Patients were allowed to  
569 taper or discontinue concomitant ITP medications after being treated with PROMACTA for  
570 6 weeks. Patients were permitted to receive rescue treatments at any time during the trial as  
571 clinically indicated. The primary endpoint was the odds of achieving a platelet count  $\geq 50 \times 10^9/L$   
572 and  $\leq 400 \times 10^9/L$  for patients receiving PROMACTA relative to placebo and was based on  
573 patient response profiles throughout the 6-month treatment period.

574 The median age of the patients treated with PROMACTA and placebo was 47 years and  
575 52.5 years, respectively. Approximately half of the patients treated with PROMACTA and  
576 placebo (47% and 50%, respectively) were receiving concomitant ITP medication  
577 (predominantly corticosteroids) at randomization and had baseline platelet counts  $\leq 15 \times 10^9/L$   
578 (50% and 48%, respectively). A similar percentage of patients treated with PROMACTA and  
579 placebo (37% and 34%, respectively) had a prior splenectomy.

580 In 134 patients who completed 26 weeks of treatment, a sustained platelet response  
581 (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  
582 treatment period in the absence of rescue medication at any time) was achieved by 60% of  
583 patients treated with PROMACTA, compared to 10% of patients treated with placebo  
584 (splenectomized patients: PROMACTA 51%, placebo 8%; non-splenectomized patients:  
585 PROMACTA 66%, placebo 11%). The proportion of responders in the PROMACTA treatment  
586 group was between 37% and 56% compared to 7% and 19% in the placebo treatment group for  
587 all on-therapy visits. Patients treated with PROMACTA were significantly more likely to  
588 achieve a platelet count between  $50 \times 10^9/L$  and  $400 \times 10^9/L$  during the entire 6-month treatment  
589 period compared to those patients treated with placebo.

590 Outcomes of treatment are presented in Table 7 for all patients enrolled in the trial.  
591

592 **Table 7. Outcomes of Treatment from Trial 3 in Adults With Chronic Immune (Idiopathic)**  
593 **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)

594

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

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

#### 604 **14.2 Chronic Hepatitis C-Associated Thrombocytopenia**

605 The efficacy and safety of PROMACTA for the treatment of thrombocytopenia in adult  
606 patients with chronic hepatitis C were evaluated in 2 randomized, double-blind, placebo-  
607 controlled trials. Trial 1 utilized peginterferon alfa-2a (PEGASYS<sup>®</sup>) plus ribavirin for antiviral  
608 treatment and Trial 2 utilized peginterferon alfa-2b (PEGINTRON<sup>®</sup>) plus ribavirin. In both trials,  
609 patients with a platelet count of  $< 75 \times 10^9/L$  were enrolled and stratified by platelet count,  
610 screening HCV RNA, and HCV genotype. Patients were excluded if they had evidence of  
611 decompensated liver disease with Child-Pugh score  $> 6$  (class B and C), history of ascites, or  
612 hepatic encephalopathy. The median age of the patients in both trials was 52 years, 63% were  
613 male, and 74% were Caucasian. Sixty-nine percent of patients had HCV genotypes 1, 4, 6 with  
614 the remainder genotypes 2 and 3. Approximately 30% of patients had been previously treated  
615 with interferon and ribavirin. The majority of patients (90%) had bridging fibrosis and cirrhosis,  
616 as indicated by noninvasive testing. A similar proportion (95%) of patients in both treatment  
617 groups had Child-Pugh level A (score 5-6) at baseline. A similar proportion of patients (2%) in  
618 both treatment groups had baseline international normalized ratio (INR)  $> 1.7$ . Median baseline  
619 platelet counts (approximately  $60 \times 10^9/L$ ) were similar in both treatment groups. The trials  
620 consisted of two phases – a pre-antiviral treatment phase and an antiviral treatment phase. In the  
621 pre-antiviral treatment phase, patients received open-label PROMACTA to increase the platelet  
622 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  
623 administered at an initial dose of 25 mg once daily for 2 weeks and increased in 25 mg  
624 increments over 2 to 3 week periods to achieve the optimal platelet count to initiate antiviral  
625 therapy. The maximal time patients could receive open-label PROMACTA was 9 weeks. If  
626 threshold platelet counts were achieved, patients were randomized (2:1) to the same dose of  
627 PROMACTA at the end of the pre-treatment phase or to placebo. PROMACTA was

628 administered in combination with pegylated interferon and ribavirin per their respective  
629 prescribing information for up to 48 weeks.

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

634 In both trials, a significantly greater proportion of patients treated with PROMACTA  
635 achieved SVR (see Table 8). The improvement in the proportion of patients who achieved SVR  
636 was consistent across subgroups based on baseline platelet count ( $< 50 \times 10^9/L$  versus  $\geq 50 \times$   
637  $10^9/L$ ). In patients with high baseline viral loads ( $\geq 800,000$ ), the SVR rate was 18% (82/452) for  
638 PROMACTA versus 8% (20/239) for placebo.

639

640 **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>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

641 <sup>a</sup> PROMACTA given in combination with peginterferon alfa-2a (180 mcg once weekly for  
642 48 weeks for genotypes 1/4/6; 24 weeks for genotype 2 or 3) plus ribavirin (800 to 1,200 mg  
643 daily in 2 divided doses orally).

644 <sup>b</sup> PROMACTA given in combination with peginterferon alfa-2b (1.5 mcg/kg once weekly for  
645 48 weeks for genotypes 1/4/6; 24 weeks for genotype 2 or 3) plus ribavirin (800 to 1,400 mg  
646 daily in 2 divided doses orally).

647 <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.

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

649

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

## 653 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

- 656 • The 25 mg tablets are round, biconvex, orange, film-coated tablets debossed with GS NX3  
657 and 25 on one side and are available in bottles of 30: NDC 0007-4640-13.
- 658 • The 50 mg tablets are round, biconvex, blue, film-coated tablets debossed with GS UFU and  
659 50 on one side and are available in bottles of 30: NDC 0007-4641-13.
- 660 • The 75 mg tablets are round, biconvex, pink, film-coated tablets debossed with GS FFS and  
661 75 on one side and are available in bottles of 30: NDC 0007-4642-13.
- 662 • The 100 mg tablets are round, biconvex, green, film-coated tablets debossed with GS 1L5  
663 and are available in bottles of 30: NDC 0007-4646-13. This product contains a desiccant.  
664 Store at room temperature between 20°C and 25°C (68°F to 77°F); excursions permitted  
665 to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not remove desiccant  
666 if present. Dispense in original bottle.

## 667 **17 PATIENT COUNSELING INFORMATION**

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

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

- 671 • For patients with chronic ITP, therapy with PROMACTA is administered to achieve and  
672 maintain a platelet count  $\geq 50 \times 10^9/L$  as necessary to reduce the risk for bleeding.
- 673 • For patients with chronic hepatitis C, therapy with PROMACTA is administered to achieve  
674 and maintain a platelet count necessary to initiate and maintain antiviral therapy with  
675 pegylated interferon and ribavirin.
- 676 • Therapy with PROMACTA may be associated with hepatobiliary laboratory abnormalities.
- 677 • Advise patients with chronic hepatitis C and cirrhosis that they may be at risk for hepatic  
678 decompensation when receiving alfa interferon therapy.
- 679 • Advise patients that they should report any of the following signs and symptoms of liver  
680 problems to their healthcare provider right away.
- 681 • yellowing of the skin or the whites of the eyes (jaundice)
- 682 • unusual darkening of the urine
- 683 • unusual tiredness
- 684 • right upper stomach area pain
- 685 • confusion
- 686 • swelling of the stomach area (abdomen)
- 687 • Advise patients that thrombocytopenia and risk of bleeding may reoccur upon discontinuing  
688 PROMACTA, particularly if PROMACTA is discontinued while the patient is on  
689 anticoagulants or antiplatelet agents.
- 690 • Advise patients that too much PROMACTA may result in excessive platelet counts and a risk  
691 for thrombotic/thromboembolic complications.
- 692 • Advise patients that during therapy with PROMACTA, they should continue to avoid  
693 situations or medications that may increase the risk for bleeding.

- 694 • Advise patients to have a baseline ocular examination prior to administration of  
695 PROMACTA and be monitored for signs and symptoms of cataracts during therapy.  
696 • Advise patients to keep at least a 4-hour interval between PROMACTA and foods, mineral  
697 supplements, and antacids which contain polyvalent cations such as iron, calcium, aluminum,  
698 magnesium, selenium, and zinc.

699

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

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705 GlaxoSmithKline

706 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 low blood platelet counts in people with:

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

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

752

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

754

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

758

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

761

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

763

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

765

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

- 767 • have liver or kidney problems
- 768 • have or had a blood clot
- 769 • have a history of cataracts
- 770 • have had surgery to remove your spleen (splenectomy)
- 771 • have bleeding problems
- 772 • are Asian and you are of Chinese, Japanese, Taiwanese, or Korean ancestry. You  
773 may need a lower dose of PROMACTA.
- 774 • have any other medical conditions
- 775 • are pregnant or plan to become pregnant. It is not known if PROMACTA will  
776 harm an unborn baby.

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

- 784 • are breastfeeding or plan to breastfeed. It is not known if PROMACTA passes  
785 into your breast milk. You and your healthcare provider should decide whether  
786 you will take PROMACTA or breastfeed. You should not do both.

787

788 **Tell your healthcare provider about all the medicines you take**, including  
789 prescription and over-the-counter medicines, vitamins, and herbal supplements.  
790 PROMACTA may affect the way certain medicines work. Certain other medicines  
791 may affect the way PROMACTA works.

792

793 Especially tell your healthcare provider if you take:

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

796

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

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

802

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

805

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

808

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

810

- 811 • Take PROMACTA exactly as your healthcare provider tells you to take it. Do not  
812 stop taking PROMACTA without talking with your healthcare provider first. Do  
813 not change your dose or schedule for taking PROMACTA unless your healthcare  
814 provider tells you to change it.
- 815 • Take PROMACTA on an empty stomach, either 1 hour before or 2 hours after  
816 eating food.
- 817 • Take PROMACTA at least 4 hours before or 4 hours after eating dairy products  
818 and calcium fortified juices.
- 819 • If you miss a dose of PROMACTA, wait and take your next scheduled dose. Do  
820 not take more than one dose of PROMACTA in one day.
- 821 • If you take too much PROMACTA, you may have a higher risk of serious side  
822 effects. Call your healthcare provider right away.
- 823 • Your healthcare provider will check your platelet count during your treatment  
824 with PROMACTA and change your dose of PROMACTA as needed.
- 825 • Tell your healthcare provider about any bruising or bleeding that happens while  
826 you take and after you stop taking PROMACTA.

827

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

829

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

831

832 **What are the possible side effects of PROMACTA?**

833

834 PROMACTA may cause serious side effects, including:

835

- 836 • See **“What is the most important information I should know about**
- 837 **PROMACTA?”**
- 838 • **Abnormal liver function tests.** Your healthcare provider will order blood tests
- 839 to check your liver before you start taking PROMACTA and during your
- 840 treatment. In some cases treatment with PROMACTA may need to be stopped
- 841 due to changes in your liver function tests.
- 842 • **High platelet counts and higher risk for blood clots.** Your risk of getting a
- 843 blood clot is increased if your platelet count is too high during treatment with
- 844 PROMACTA. Your risk of getting a blood clot may also be increased during
- 845 treatment with PROMACTA if you have normal or low platelet counts. You may
- 846 have severe problems or die from some forms of blood clots, such as clots that
- 847 travel to the lungs or that cause heart attacks or strokes. Your healthcare
- 848 provider will check your blood platelet counts, and change your dose or stop
- 849 PROMACTA if your platelet counts get too high. Tell your healthcare provider
- 850 right away if you have signs and symptoms of a blood clot in the leg, such as
- 851 swelling, pain, or tenderness in your leg.
- 852 People with chronic liver disease may be at risk for a type of blood clot in the
- 853 stomach area. Tell your healthcare provider right away if you have stomach area
- 854 pain that may be a symptom of this type of blood clot.
- 855 • **New or worsened cataracts (a clouding of the lens in the eye).** New or
- 856 worsened cataracts have happened in people taking PROMACTA. Your healthcare
- 857 provider will check your eyes before and during your treatment with PROMACTA.
- 858 Tell your healthcare provider about any changes in your eyesight while taking
- 859 PROMACTA.

860

861 **The most common side effects of PROMACTA when used to treat chronic**

862 **ITP are:**

- 863 • nausea
- 864 • diarrhea
- 865 • upper respiratory tract infection. Symptoms may include runny nose, stuffy
- 866 nose, and sneezing
- 867 • vomiting
- 868 • muscle aches
- 869 • urinary tract infection. Symptoms may include frequent or urgent need to
- 870 urinate, low fever in some people, pain or burning with urination.
- 871 • pain or swelling (inflammation) in your throat or mouth (oropharyngeal pain and

- 872 pharyngitis)
- 873 • abnormal liver function tests
- 874 • back pain
- 875 • "flu" like symptoms (influenza) including fever, headache, tiredness, cough, sore
- 876 throat, and body aches
- 877 • skin tingling, itching, or burning
- 878 • rash
- 879

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

- 882 • low red blood cell count (anemia)
- 883 • fever
- 884 • tiredness
- 885 • headache
- 886 • nausea
- 887 • diarrhea
- 888 • decreased appetite
- 889 • "flu" like symptoms (influenza) including fever, headache, tiredness, cough, sore
- 890 throat, and body aches
- 891 • feeling weak
- 892 • trouble sleeping
- 893 • cough
- 894 • itching
- 895 • chills
- 896 • muscle aches
- 897 • hair loss
- 898 • swelling in your ankles, feet, and legs
- 899

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

902

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

905

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

908

909 **How should I store PROMACTA tablets?**

910

- 911 • Store PROMACTA at room temperature between 68°F to 77°F (20°C to 25°C).

- 912 • Keep PROMACTA tightly closed in the bottle given to you.  
913 • The PROMACTA bottle may contain a desiccant pack to help keep your medicine  
914 dry. Do not remove the desiccant pack from the bottle.

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

916

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

918

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

923

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

928

929 For more information about PROMACTA, go to [www.PROMACTA.com](http://www.PROMACTA.com) or call 1-888-  
930 825-5249.

931

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

933

934 **Active ingredient:** eltrombopag olamine.

### 935 **Inactive ingredients:**

- 936 • **Tablet Core:** magnesium stearate, mannitol, microcrystalline cellulose,  
937 povidone, and sodium starch glycolate.
- 938 • **Coating:** hypromellose (12.5 mg, 25 mg, 50 mg, and 75 mg tablets) or  
939 polyvinyl alcohol and talc (100 mg tablet), polyethylene glycol 400, titanium  
940 dioxide, polysorbate 80 (12.5 mg tablet), and FD&C Yellow No. 6 aluminum lake  
941 (25 mg tablet), FD&C Blue No. 2 aluminum lake (50 mg tablet), Iron Oxide Red  
942 and Iron Oxide Black (75 mg tablet), or Iron Oxide Yellow and Iron Oxide Black  
943 (100 mg tablet).

944

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

947

948 PROMACTA is a registered trademark of the GSK group of companies.

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951 GlaxoSmithKline

952 Research Triangle Park, NC 27709

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956 Revised: Month YEAR

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/s/  
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ROBERT C KANE  
04/10/2014