

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PROMACTA safely and effectively. See full prescribing information for PROMACTA.

PROMACTA® (eltrombopag) Tablets

For oral use

Initial U.S. Approval: 2008

WARNING: RISK FOR HEPATOTOXICITY

See full prescribing information for complete boxed warning

PROMACTA may cause hepatotoxicity:

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

RECENT MAJOR CHANGES

Dosage and Administration, Initial Dose Regimen. (2.1) XX/2011

Warnings and Precautions, Thrombotic/Thromboembolic Complications. (5.4) XX/2011

INDICATIONS AND USAGE

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

PROMACTA should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding. PROMACTA should not be used in an attempt to normalize platelet counts. (1)

DOSAGE AND ADMINISTRATION

- The initial dose of PROMACTA is 50 mg once daily for most patients. (2)
- Reduce the initial dose in patients with hepatic impairment (Child-Pugh Class A, B, C) and/or patients of East Asian ancestry. (2.1)
- Give on an empty stomach (1 hour before or 2 hours after a meal). (2)
- Allow a 4-hour interval between PROMACTA and other medications, foods, or supplements containing polyvalent cations (e.g., iron, calcium, aluminum, magnesium, selenium, and zinc). (2, 7.4)
- Adjust the daily dose to achieve and maintain a platelet count $\geq 50 \times 10^9/L$ in order to reduce the risk for bleeding. (2)
- Do not exceed a daily dose of 75 mg. (2)
- Discontinue PROMACTA if the platelet count does not increase after 4 weeks at the maximum dose; also discontinue PROMACTA for important liver test abnormalities or excessive platelet count responses. (2)

DOSAGE FORMS AND STRENGTHS

25 mg, 50 mg, and 75 mg tablets. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to 25 mg, 50 mg, or 75 mg of eltrombopag free acid. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- PROMACTA may cause hepatotoxicity. Increases in serum aminotransferase levels and bilirubin were observed. Liver chemistries must be measured before the initiation of treatment and regularly during treatment. (5.1)
- PROMACTA is a thrombopoietin receptor agonist and TPO-receptor agonists increase the risk for development or progression of reticulin fiber deposition within the bone marrow. Monitor peripheral blood for signs of marrow fibrosis. (5.2)
- Discontinuation may result in recurrence of thrombocytopenia. Monitor weekly complete blood counts (CBCs), including platelet counts for at least 4 weeks after discontinuation. (5.3)
- Excessive doses of PROMACTA may increase platelet counts to a level that produces thrombotic/thromboembolic complications. (5.4)
- PROMACTA may increase the risk for hematological malignancies, especially in patients with myelodysplastic syndrome. (5.5)
- Monitor CBCs, including platelet counts and peripheral blood smears, weekly during the dose adjustment phase of therapy with PROMACTA and then monthly following establishment of a stable dose of PROMACTA. (5.6)
- Because of the risk for hepatotoxicity and other risks, PROMACTA is available only through a restricted distribution program. To enroll in the restricted distribution program, PROMACTA CARES, call 1-877-9-PROMACTA (1-877-977-6622). (5.8)

ADVERSE REACTIONS

The most common adverse reactions (occurring in $\geq 3\%$ of patients receiving PROMACTA and at a higher rate in PROMACTA versus placebo) were: nausea, diarrhea, upper respiratory tract infection, vomiting, increased ALT, myalgia, urinary tract infection, oropharyngeal pain, increased AST, pharyngitis, back pain, influenza, paresthesia, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Eltrombopag is an inhibitor of OATP1B1 and BCRP transporters. Monitor patients closely for signs and symptoms of excessive exposure to the drugs that are substrates of OATP1B1 and BCRP (e.g., rosuvastatin) and consider reduction of the dose of these drugs. (7.2)
- Polyvalent cations (e.g., iron, calcium, aluminum, magnesium, selenium, and zinc) significantly reduce the absorption of eltrombopag; PROMACTA must not be taken within 4 hours of any medications or products containing polyvalent cations such as antacids, dairy products, and mineral supplements. (7.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: PROMACTA may cause fetal harm. Enroll pregnant patients in the PROMACTA pregnancy registry by calling 1-888-825-5249. (8.1)
- Nursing Mothers: A decision should be made to discontinue PROMACTA or nursing, taking into account the importance of PROMACTA to the mother. (8.3)
- Reduce the initial dose in patients with hepatic impairment (Child-Pugh Class A, B, C). (8.6)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE.

Revised: Month/YEAR

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FULL PRESCRIBING INFORMATION

1 **WARNING: RISK FOR HEPATOTOXICITY**

2 **PROMACTA may cause hepatotoxicity:**

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

17 **Because of the risk for hepatotoxicity and other risks [see Warnings and Precautions (5.1-**
18 **5.6)], PROMACTA is available only through a restricted distribution program called**
19 **PROMACTA CARES. Under PROMACTA CARES, only prescribers, pharmacies, and**
20 **patients registered with the program are able to prescribe, dispense, and receive**
21 **PROMACTA. To enroll in PROMACTA CARES, call 1-877-9-PROMACTA [see Warnings**
22 **and Precautions (5.8)].**

23 **1 INDICATIONS AND USAGE**

24 PROMACTA is indicated for the treatment of thrombocytopenia in patients with chronic
25 immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to
26 corticosteroids, immunoglobulins, or splenectomy. PROMACTA should be used only in patients
27 with ITP whose degree of thrombocytopenia and clinical condition increases the risk for
28 bleeding. PROMACTA should not be used in an attempt to normalize platelet counts.

29 **2 DOSAGE AND ADMINISTRATION**

30 Only prescribers enrolled in PROMACTA CARES may prescribe PROMACTA [see
31 Warnings and Precautions (5.8)].

32 Monitor liver tests (ALT, AST, and bilirubin) and complete blood counts (CBCs),
33 including platelet counts and peripheral blood smears, prior to initiation of PROMACTA and
34 throughout therapy with PROMACTA. If bilirubin is elevated, perform fractionation. Monitor
35 CBCs, including platelet counts, for at least 4 weeks following discontinuation of PROMACTA
36 [see Warnings and Precautions (5.3)]. In clinical studies, platelet counts generally increased

37 within 1 to 2 weeks after starting PROMACTA and decreased within 1 to 2 weeks after
38 discontinuing PROMACTA [see *Clinical Studies (14)*].

39 Use the lowest dose of PROMACTA to achieve and maintain a platelet count $\geq 50 \times$
40 $10^9/L$ as necessary to reduce the risk for bleeding. Dose adjustments are based upon the platelet
41 count response. Do not use PROMACTA in an attempt to normalize platelet counts [see
42 *Warnings and Precautions (5.4)*].

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

48 **2.1 Initial Dose Regimen**

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

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

54 For patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B,
55 C), initiate PROMACTA at a reduced dose of 25 mg once daily [see *Use in Specific Populations*
56 *(8.6)*].

57 For patients of East Asian ancestry with hepatic impairment (Child-Pugh Class A, B, C),
58 initiate PROMACTA at a reduced dose of 25 mg once every other day [see *Clinical*
59 *Pharmacology (12.3)*].

60 **2.2 Monitoring and Dose Adjustment**

61 After initiating PROMACTA, adjust the dose to achieve and maintain a platelet count
62 $\geq 50 \times 10^9/L$ as necessary to reduce the risk for bleeding. Do not exceed a dose of 75 mg daily.
63 Monitor clinical hematology and liver tests regularly throughout therapy with PROMACTA and
64 modify the dosage regimen of PROMACTA based on platelet counts as outlined in Table 1.
65 During therapy with PROMACTA, assess CBCs, including platelet count and peripheral blood
66 smears, weekly until a stable platelet count has been achieved. Obtain CBCs including platelet
67 counts and peripheral blood smears, monthly thereafter.

68

69 **Table 1. Dose Adjustments of PROMACTA**

Platelet Count Result	Dose Adjustment or Response
<50 x 10 ⁹ /L following at least 2 weeks of PROMACTA	Increase daily dose by 25 mg to a maximum of 75 mg/day. ^a
≥200 x 10 ⁹ /L to ≤400 x 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 x 10 ⁹ /L	Stop PROMACTA; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is <150 x 10 ⁹ /L, reinstitute therapy at a daily dose reduced by 25 mg.
>400 x 10 ⁹ /L after 2 weeks of therapy at lowest dose of PROMACTA	Discontinue PROMACTA.

^a For patients taking 25 mg once every other day; increase the dose to 25 mg daily before increasing the dose amount by 25 mg.

70
 71 In patients with hepatic impairment (Child-Pugh Class A, B, C), after initiating
 72 PROMACTA or after any subsequent dosing increase wait 3 weeks before increasing the dose.
 73 Modify the dosage regimen of concomitant ITP medications, as medically appropriate, to
 74 avoid excessive increases in platelet counts during therapy with PROMACTA. Do not administer
 75 more than one dose of PROMACTA within any 24-hour period.

76 **2.3 Discontinuation**

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

82 **3 DOSAGE FORMS AND STRENGTHS**

83 25 mg tablets — round, biconvex, orange, film-coated tablets debossed with GS NX3 and
 84 25 on one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to
 85 25 mg of eltrombopag free acid.

86 50 mg tablets — round, biconvex, blue, film-coated tablets debossed with GS UFU and
 87 50 on one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to
 88 50 mg of eltrombopag free acid.

89 75 mg tablets — round, biconvex, pink, film-coated tablets debossed with GS FSS and
 90 75 on one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to
 91 75 mg of eltrombopag free acid.

92 **4 CONTRAINDICATIONS**

93 None.

94 **5 WARNINGS AND PRECAUTIONS**

95 **5.1 Risk for Hepatotoxicity**

96 PROMACTA administration may cause hepatotoxicity. In the controlled clinical studies,
97 one patient experienced Grade 4 (NCI Common Terminology Criteria for Adverse Events [NCI
98 CTCAE] toxicity scale) elevations in serum liver test values during therapy with PROMACTA,
99 worsening of underlying cardiopulmonary disease, and death. One patient in the placebo group
100 experienced a Grade 4 liver test abnormality. Overall, serum liver test abnormalities
101 (predominantly Grade 2 or less in severity) were reported in 11% and 7% of the PROMACTA
102 and placebo groups, respectively. In the 3 controlled studies, four patients (1%) treated with
103 PROMACTA and three patients in the placebo group (2%) discontinued treatment due to
104 hepatobiliary laboratory abnormalities. Seven of the patients treated with PROMACTA in the
105 controlled studies with hepatobiliary laboratory abnormalities were re-exposed to PROMACTA
106 in the extension study. Six of these patients again experienced liver test abnormalities
107 (predominantly Grade 1) resulting in discontinuation of PROMACTA in one patient. In the
108 extension study, one additional patient had PROMACTA discontinued due to liver test
109 abnormalities (\leq Grade 3).

110 Measure serum ALT, AST, and bilirubin prior to initiation of PROMACTA, every
111 2 weeks during the dose adjustment phase, and monthly following establishment of a stable dose.
112 If bilirubin is elevated, perform fractionation. Evaluate abnormal serum liver tests with repeat
113 testing within 3 to 5 days. If the abnormalities are confirmed, monitor serum liver tests weekly
114 until the abnormality(ies) resolve, stabilize, or return to baseline levels. Discontinue
115 PROMACTA if ALT levels increase to $\geq 3X$ the upper limit of normal (ULN) and are:

- 116
- 117 • progressive, or
 - 118 • persistent for ≥ 4 weeks, or
 - 119 • accompanied by increased direct bilirubin, or
 - 120 • accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation.

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

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

131 **5.2 Bone Marrow Reticulin Formation and Risk for Bone Marrow Fibrosis**

132 PROMACTA is a thrombopoietin (TPO) receptor agonist and TPO-receptor agonists
133 increase the risk for development or progression of reticulin fiber deposition within the bone
134 marrow.

135 In the extension study, 151 patients have had bone marrow biopsies evaluated for
136 increased reticulin and collagen fiber deposition. Bone marrow biopsies taken after 1 year of
137 therapy showed predominantly myelofibrosis (MF) Grade 1 or less in 140/151 (93%) of patients.
138 There were 11/151 (7%) of patients with MF Grade 2. Four patients had collagen deposition
139 reported. One patient with a preexisting MF Grade 1 developed a MF Grade 2 and subsequently
140 discontinued treatment with PROMACTA. Clinical studies have not excluded a risk of bone
141 marrow fibrosis with cytopenias.

142 Prior to initiation of PROMACTA, examine the peripheral blood smear closely to
143 establish a baseline level of cellular morphologic abnormalities. Following identification of a
144 stable dose of PROMACTA, examine peripheral blood smears and CBCs monthly for new or
145 worsening morphological abnormalities (e.g., teardrop and nucleated red blood cells, immature
146 white blood cells) or cytopenias. If the patient develops new or worsening morphological
147 abnormalities or cytopenias, discontinue treatment with PROMACTA and consider a bone
148 marrow biopsy, including staining for fibrosis.

149 **5.3 Recurrence of Thrombocytopenia and Hemorrhage Risk After Cessation of**
150 **PROMACTA**

151 Discontinuation of PROMACTA may result in recurrence of thrombocytopenia. This
152 recurrence of thrombocytopenia may increase the patient's risk of bleeding, particularly if
153 PROMACTA is discontinued while the patient is on anticoagulants or antiplatelet agents. In the
154 3 controlled clinical studies, transient decreases in platelet counts to levels lower than baseline
155 were observed following discontinuation of treatment in 8% of patients in both the PROMACTA
156 and placebo groups. Serious hemorrhagic events requiring the use of supportive ITP medications
157 occurred in 4 severely thrombocytopenic patients within one month following the
158 discontinuation of PROMACTA; none were reported among patients in the placebo group.

159 Following discontinuation of PROMACTA, obtain weekly CBCs, including platelet
160 counts for at least 4 weeks and consider alternative treatments for recurrence of
161 thrombocytopenia, according to current treatment guidelines [*see Adverse Reactions (6.1)*].

162 **5.4 Thrombotic/Thromboembolic Complications**

163 Thrombotic/thromboembolic complications may result from excessive increases in
164 platelet counts. Excessive doses of PROMACTA may increase platelet counts to a level that
165 produces thrombotic/thromboembolic complications.

166 In the 3 controlled clinical studies, thrombotic/thromboembolic complications occurred in
167 four patients in the groups that received PROMACTA and none in the placebo groups.
168 Thrombotic/thromboembolic complications were also reported in the extension study. The
169 thrombotic/thromboembolic complications included both venous and arterial events and were
170 observed at low and normal platelet counts.

171 Use caution when administering PROMACTA to patients with known risk factors for
172 thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, chronic
173 liver disease). To minimize the risk for thrombotic/thromboembolic complications, do not use
174 PROMACTA in an attempt to normalize platelet counts. Follow the dose adjustment guidelines
175 to achieve and maintain a platelet count of $\geq 50 \times 10^9/L$ as necessary to decrease the risk for
176 bleeding [*see Dosage and Administration (2.2)*].

177 In a controlled study in non-ITP thrombocytopenic patients with chronic liver disease
178 undergoing elective invasive procedures (N = 292), the risk of thrombotic events was increased
179 in patients treated with 75 mg PROMACTA once daily. Seven thrombotic complications (six
180 patients) were reported in the group that received PROMACTA and three thrombotic
181 complications were reported in the placebo group (two patients). All of the thrombotic
182 complications reported in the group that received PROMACTA were of the portal venous
183 system. Five of the six patients in the group that received PROMACTA experienced a
184 thrombotic complication within 30 days of completing treatment with PROMACTA and at a
185 platelet count above $200 \times 10^9/L$. The risk of portal venous thrombosis was increased in
186 thrombocytopenic patients with chronic liver disease treated with 75 mg PROMACTA once
187 daily for 2 weeks in preparation for invasive procedures.

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

193 **5.5 Hematologic Malignancies and Progression of Malignancies**

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

201 **5.6 Laboratory Monitoring**

202 Complete Blood Counts (CBCs): Monitor CBCs, including platelet counts and
203 peripheral blood smears, prior to initiation, throughout, and following discontinuation of therapy
204 with PROMACTA. Prior to the initiation of PROMACTA, examine the peripheral blood
205 differential to establish the extent of red and white blood cell abnormalities. Obtain CBCs,
206 including platelet counts and peripheral blood smears, weekly during the dose adjustment phase
207 of therapy with PROMACTA and then monthly following establishment of a stable dose of
208 PROMACTA. Obtain CBCs, including platelet counts, weekly for at least 4 weeks following
209 discontinuation of PROMACTA [*see Dosage and Administration (2) and Warnings and*
210 *Precautions (5.2, 5.3)*].

211 **Liver Tests:** Monitor serum liver tests (ALT, AST, and bilirubin) prior to initiation of
212 PROMACTA, every 2 weeks during the dose adjustment phase, and monthly following
213 establishment of a stable dose. If bilirubin is elevated, perform fractionation. If abnormal levels
214 are detected, repeat the tests within 3 to 5 days. If the abnormalities are confirmed, monitor
215 serum liver tests weekly until the abnormality(ies) resolve, stabilize, or return to baseline levels.
216 Discontinue PROMACTA for the development of important liver test abnormalities [*see*
217 *Warnings and Precautions (5.1)*].

218 **5.7 Cataracts**

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

226 **5.8 PROMACTA Distribution Program**

227 PROMACTA is available only through a restricted distribution program called
228 PROMACTA CARES. Under PROMACTA CARES, only prescribers, pharmacies, and patients
229 registered with the program are able to prescribe, dispense, and receive PROMACTA. This
230 program provides educational materials and a mechanism for the proper use of PROMACTA. To
231 enroll in PROMACTA CARES, call 1-877-9-PROMACTA (1-877-977-6622). Prescribers and
232 patients are required to understand the risks of therapy with PROMACTA. Prescribers are
233 required to understand the information in the prescribing information and be able to:

- 234 • Educate patients on the benefits and risks of treatment with PROMACTA, ensure that the
235 patient receives the Medication Guide, instruct them to read it, and encourage them to ask
236 questions when considering PROMACTA. Patients may be educated by the enrolled
237 prescriber or a healthcare provider under that prescriber's direction.
- 238 • Review the PROMACTA CARES Prescriber Enrollment Forms, sign the form, and return the
239 form according to PROMACTA CARES Program instructions.
- 240 • As part of the initial prescription process for PROMACTA, obtain the patient's signature on
241 the Patient Enrollment and Consent form, sign it, place the original signed form in the
242 patient's medical record, send a copy to PROMACTA CARES, and give a copy to the patient.
- 243 • Report any serious adverse events associated with the use of PROMACTA to PROMACTA
244 CARES Call Center at 1-877-9-PROMACTA (1-877-977-6622) or to the FDA's MedWatch
245 Program at 1-800-FDA-1088.
- 246 • Report serious adverse events observed in patients receiving PROMACTA, including events
247 actively solicited at 6-month intervals.

248 **6 ADVERSE REACTIONS**

249 **6.1 Clinical Trials Experience**

250 In clinical studies, hemorrhage was the most common serious adverse reaction and most
251 hemorrhagic reactions followed discontinuation of PROMACTA. Other serious adverse
252 reactions included liver test abnormalities and thrombotic/thromboembolic complications [*see*
253 *Warnings and Precautions (5.1, 5.4)*].

254 The data described below reflect PROMACTA exposure to 446 patients with chronic ITP
255 aged 18 to 85, of whom 65% were female across the ITP clinical development program including
256 3 placebo-controlled studies. PROMACTA was administered to 277 patients for at least
257 6 months and 202 patients for at least 1 year.

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

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

264

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

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

266

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

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

274

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

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

276

277 In a placebo-controlled trial of eltrombopag in non-ITP thrombocytopenic patients with
 278 chronic liver disease (CLD), six eltrombopag-treated patients and one patient in the placebo
 279 group developed portal vein thromboses [see *Warnings and Precautions (5.4)*].

280 **7 DRUG INTERACTIONS**

281 **7.1 Cytochrome P450**

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

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

296 **7.2 Transporters**

297 *In vitro* studies demonstrate that eltrombopag is an inhibitor of the organic anion
 298 transporting polypeptide OATP1B1 and breast cancer resistance protein (BCRP) and can

299 increase the systemic exposure of other drugs that are substrates of these transporters (e.g.,
300 benzylpenicillin, atorvastatin, fluvastatin, pravastatin, rosuvastatin, methotrexate, nateglinide,
301 repaglinide, rifampin, doxorubicin). Administration of 75 mg of PROMACTA once daily for
302 5 days with a single 10 mg dose of the OATP1B1 and BCRP substrate, rosuvastatin, to 39
303 healthy adult subjects increased plasma rosuvastatin $AUC_{0-\infty}$ by 55% and C_{max} by 103%.

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

309 *In vitro* studies demonstrate that eltrombopag is a BCRP substrate. The effect of co-
310 administration of PROMACTA with moderate or strong BCRP inhibitors or inducers on the
311 systemic exposure of PROMACTA has not been evaluated in clinical studies. Monitor patients
312 closely for signs or symptoms of excessive exposure to PROMACTA when concomitantly
313 administered with moderate or strong inhibitors of BCRP.

314 **7.3 UDP-glucuronosyltransferases (UGTs)**

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

322 *In vitro* studies demonstrate that UGT1A1 and UGT1A3 are responsible for the
323 glucuronidation of PROMACTA. The significance of coadministration of PROMACTA with
324 moderate or strong inhibitors or inducers on the systemic exposure of PROMACTA has not been
325 evaluated in clinical studies. Monitor patients closely for signs or symptoms of excessive
326 exposure to PROMACTA when concomitantly administered with moderate or strong inhibitors
327 of UGT1A1 or UGT1A3.

328 **7.4 Polyvalent Cations (Chelation)**

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

338 **8 USE IN SPECIFIC POPULATIONS**

339 **8.1 Pregnancy**

340 Pregnancy Category C

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

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

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

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

357 Pregnant rabbits were treated with oral eltrombopag doses of 30, 80, or 150 mg/kg/day
358 (0.04, 0.3, and 0.5 times the human clinical exposure based on AUC). No evidence of
359 fetotoxicity, embryoletality, or teratogenicity was observed.

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

365 **8.3 Nursing Mothers**

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

370 **8.4 Pediatric Use**

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

372 **8.5 Geriatric Use**

373 Of the 106 patients in 2 randomized clinical studies of PROMACTA 50 mg dose, 22%
374 were 65 years of age and older, and 9% were 75 years of age and older. No overall differences in
375 safety or efficacy have been observed between older and younger patients in the placebo-
376 controlled studies, but greater sensitivity of some older individuals cannot be ruled out. In
377 general, dose adjustment for an elderly patient should be cautious, reflecting the greater

378 frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other
379 drug therapy.

380 **8.6 Hepatic Impairment**

381 The disposition of PROMACTA following a single 50 mg dose in patients with mild,
382 moderate, and severe hepatic impairment was compared to subjects with normal hepatic
383 function. The degree of hepatic impairment was based on Child-Pugh score. Plasma eltrombopag
384 $AUC_{0-\infty}$ was 41% higher in patients with mild hepatic impairment (Child-Pugh A) compared to
385 subjects with normal hepatic function. Plasma eltrombopag $AUC_{0-\infty}$ was approximately 2-fold
386 higher in patients with moderate (Child-Pugh B) and severe hepatic impairment (Child-Pugh C).
387 The half-life of PROMACTA was prolonged 2-fold in these patients. This clinical study did not
388 evaluate protein binding effects.

389 Similar results were seen in a population pharmacokinetic (PK) analysis in
390 thrombocytopenic patients with chronic liver disease following repeat doses of eltrombopag.
391 However, compared to healthy volunteers, the population PK analysis demonstrated that mild
392 hepatic impairment resulted in an 87% to 110% higher plasma eltrombopag $AUC_{(0-\tau)}$ and patients
393 with moderate hepatic impairment had approximately 141% to 240% higher plasma eltrombopag
394 $AUC_{(0-\tau)}$ values. The half-life of PROMACTA was prolonged 3-fold in patients with mild
395 hepatic impairment and 4-fold in patients with moderate hepatic impairment. This clinical study
396 did not evaluate protein binding effects.

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

400 **8.7 Renal Impairment**

401 The disposition of a single 50 mg dose of PROMACTA in patients with mild, moderate
402 and severe renal impairment was compared to subjects with normal renal function. Average total
403 plasma eltrombopag $AUC_{0-\infty}$ was 32% to 36% lower in subjects with mild to moderate renal
404 impairment and 60% lower in subjects with severe renal impairment compared with healthy
405 subjects. The effect of renal impairment on unbound (active) eltrombopag exposure, has not been
406 assessed.

407 No adjustment in the initial PROMACTA dose is needed for patients with renal
408 impairment. Closely monitor patients with impaired renal function when administering
409 PROMACTA.

410 **10 OVERDOSAGE**

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

413 In one report, a subject who ingested 5,000 mg of PROMACTA had a platelet count
414 increase to a maximum of $929 \times 10^9/L$ at 13 days following the ingestion. The patient also
415 experienced rash, bradycardia, ALT/AST elevations, and fatigue. The patient was treated with
416 gastric lavage, oral lactulose, intravenous fluids, omeprazole, atropine, furosemide, calcium,

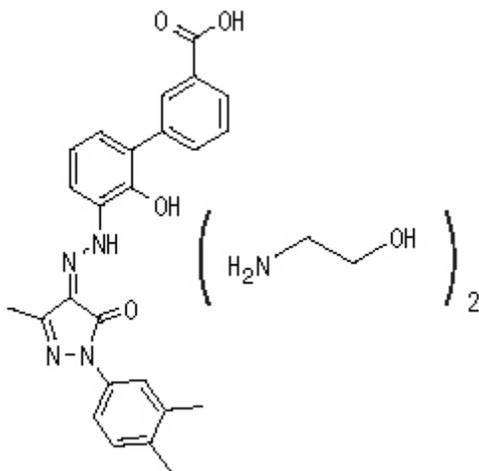
417 dexamethasone, and plasmapheresis; however, the abnormal platelet count and liver test
418 abnormalities persisted for 3 weeks. After 2 months follow-up, all events had resolved without
419 sequelae.

420 In case of an overdose, consider oral administration of a metal cation-containing
421 preparation, such as calcium, aluminum, or magnesium preparations to chelate eltrombopag and
422 thus limit absorption. Closely monitor platelet counts. Reinitiate treatment with PROMACTA in
423 accordance with dosing and administration recommendations [see *Dosage and Administration*
424 (2.2)].

425 11 DESCRIPTION

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

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



437 Eltrombopag olamine is practically insoluble in aqueous buffer across a pH range of 1 to
438 7.4, and is sparingly soluble in water.

440 The inactive ingredients of PROMACTA are: **Tablet Core:** magnesium stearate,
441 mannitol, microcrystalline cellulose, povidone, and sodium starch glycolate. **Coating:**
442 hypromellose, polyethylene glycol 400, titanium dioxide, and FD&C Yellow No. 6 aluminum
443 lake (25 mg tablet), FD&C Blue No. 2 aluminum lake (50 mg tablet), or Iron Oxide Red and Iron
444 Oxide Black (75 mg tablet).

445 **12 CLINICAL PHARMACOLOGY**

446 **12.1 Mechanism of Action**

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

450 **12.3 Pharmacokinetics**

451 A population pharmacokinetic model analysis suggests that the pharmacokinetic profile
452 for eltrombopag following oral administration is best described by a 2-compartment model.
453 Based on this model, the estimated exposures of eltrombopag after administration to patients
454 with ITP are shown in Table 3.

455
456 **Table 3. Geometric Mean (95% Confidence Intervals) of Steady-State Plasma Eltrombopag**
457 **Pharmacokinetic Parameters in Adults With Idiopathic Thrombocytopenic Purpura**

Regimen of PROMACTA	AUC_(0-τ) (mcg.hr/mL)	C_{max} (mcg/mL)
50 mg once daily (N = 34)	108 (88, 134)	8.01 (6.73, 9.53)
75 mg once daily (N = 26)	168 (143, 198)	12.7 (11.0, 14.5)

458
459 **Absorption:** Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours
460 after oral administration. Based on urinary excretion and biotransformation products eliminated
461 in feces, the oral absorption of drug-related material following administration of a single 75 mg
462 solution dose was estimated to be at least 52%.

463 An open-label, randomized, crossover study was conducted to assess the effect of food on
464 the bioavailability of eltrombopag. A standard high-fat breakfast significantly decreased plasma
465 eltrombopag AUC_{0-∞} by approximately 59% and C_{max} by 65% and delayed t_{max} by 1 hour. The
466 calcium content of this meal may have also contributed to this decrease in exposure.

467 **Distribution:** The concentration of eltrombopag in blood cells is approximately 50% to
468 79% of plasma concentrations based on a radiolabel study. *In vitro* studies suggest that
469 eltrombopag is highly bound to human plasma proteins (>99%). Eltrombopag is a substrate of
470 BCRP, but is not a substrate for P-glycoprotein (P-gp) or OATP1B1.

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

476 **Elimination:** The predominant route of eltrombopag excretion is via feces (59%), and
477 31% of the dose is found in the urine. Unchanged eltrombopag in feces accounts for
478 approximately 20% of the dose; unchanged eltrombopag is not detectable in urine. The plasma

479 elimination half-life of eltrombopag is approximately 21 to 32 hours in healthy subjects and 26
480 to 35 hours in ITP patients.

481 **Race:** The influence of East Asian ethnicity (i.e., Japanese, Chinese, Taiwanese, and
482 Korean) on the pharmacokinetics of eltrombopag was evaluated using a population
483 pharmacokinetic approach in 111 healthy adults (31 East Asians) and 88 patients with ITP (18
484 East Asians). After adjusting for body weight differences, East Asians had approximately 50%
485 higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to non-East Asian patients who were
486 predominantly Caucasian. In a separate population PK analysis of PROMACTA in 28 healthy
487 adults (non-East Asians) and 79 patients with chronic liver disease (45 East Asians), East Asian
488 patients had approximately 110% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to
489 non-East Asian patients, after adjusting for body weight differences. A reduction in the initial
490 dose of PROMACTA is recommended for patients of East Asian ancestry and East Asian
491 patients with hepatic impairment (Child-Pugh Class A, B, C) [see *Dosage and Administration*
492 (2.1)].

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

497 **Gender:** The influence of gender on the pharmacokinetics of eltrombopag was evaluated
498 using a population pharmacokinetic approach in 111 healthy adults (14 females) and 88 patients
499 with ITP (57 females). After adjustment for body weight differences females had approximately
500 23% higher plasma eltrombopag $AUC_{(0-\tau)}$ values than males.

501 **12.6 QT/QTc Prolongation**

502 There is no indication of a QT/QTc prolonging effect of PROMACTA at doses up to
503 150 mg daily for 5 days. The effects of PROMACTA at doses up to 150 mg daily for 5 days
504 (supratherapeutic doses) on the QT/QTc interval was evaluated in a double-blind, randomized,
505 placebo- and positive-controlled (moxifloxacin 400 mg, single oral dose) crossover trial in
506 healthy adult subjects. Assay sensitivity was confirmed by significant QTc prolongation by
507 moxifloxacin.

508 **13 NONCLINICAL TOXICOLOGY**

509 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

514 Eltrombopag was not mutagenic or clastogenic in a bacterial mutation assay or in 2 *in*
515 *vivo* assays in rats (micronucleus and unscheduled DNA synthesis, 10 times the human clinical
516 exposure based on C_{max}). In the *in vitro* mouse lymphoma assay, eltrombopag was marginally
517 positive (<3-fold increase in mutation frequency).

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

522 **13.2 Animal Pharmacology/Toxicology**

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

525 Treatment-related cataracts were detected in rodents in a dose- and time-dependent
526 manner. At ≥ 6 times the human clinical exposure based on AUC, cataracts were observed in
527 mice after 6 weeks and in rats after 28 weeks of dosing. At ≥ 4 times the human clinical exposure
528 based on AUC, cataracts were observed in mice after 13 weeks and in rats after 39 weeks of
529 dosing. The clinical relevance of these findings is unknown [*see Warnings and Precautions*
530 (5.7)].

531 Renal tubular toxicity was observed in studies up to 14 days in duration in mice and rats
532 at exposures that were generally associated with morbidity and mortality. Tubular toxicity was
533 also observed in a 2-year oral carcinogenicity study in mice at doses of 25, 75, and
534 150 mg/kg/day. The exposure at the lowest dose was 1.2 times the human clinical exposure
535 based on AUC. No similar effects were observed in mice after 13 weeks at exposures greater
536 than those associated with renal changes in the 2-year study, suggesting that this effect is both
537 dose- and time-dependent.

538 **14 CLINICAL STUDIES**

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

542 **14.1 Studies 1 and 2**

543 In studies 1 and 2, patients who had completed at least one prior ITP therapy and who
544 had a platelet count $< 30 \times 10^9/L$ were randomized to receive either PROMACTA or placebo
545 daily for up to 6 weeks, followed by 6 weeks off therapy. During the studies, PROMACTA or
546 placebo was discontinued if the platelet count exceeded $200 \times 10^9/L$. The primary efficacy
547 endpoint was response rate, defined as a shift from a baseline platelet count of $< 30 \times 10^9/L$ to
548 $\geq 50 \times 10^9/L$ at any time during the treatment period.

549 The median age of the patients was 50 years and 60% were female. Approximately 70%
550 of the patients had received at least 2 prior ITP therapies (predominantly corticosteroids,
551 immunoglobulins, rituximab, cytotoxic therapies, danazol, and azathioprine) and 40% of the
552 patients had undergone splenectomy. The median baseline platelet counts (approximately $18 \times$
553 $10^9/L$) were similar among all treatment groups.

554 Study 1 randomized 114 patients (2:1) to PROMACTA 50 mg or placebo. Study 2
555 randomized 117 patients (1:1:1:1) among placebo or 1 of 3 dose regimens of PROMACTA,
556 30 mg, 50 mg, or 75 mg each administered daily.

557 Table 4 shows for each study the primary efficacy outcomes for the placebo groups and
558 the patient groups who received the 50 mg daily regimen of PROMACTA.

559

560 **Table 4. Studies 1 and 2 Platelet Count Response ($\geq 50 \times 10^9/L$) Rates**

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

561 ^a *P* value <0.001 for PROMACTA versus placebo.

562

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

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

574 **14.2 Study 3**

575 In this study, 197 patients were randomized (2:1) to receive either PROMACTA 50 mg
576 once daily ($n = 135$) or placebo ($n = 62$) for 6 months, during which time the dose of
577 PROMACTA could be adjusted based on individual platelet counts. Patients were allowed to
578 taper or discontinue concomitant ITP medications after being treated with PROMACTA for
579 6 weeks. Patients were permitted to receive rescue treatments at any time during the study as
580 clinically indicated. The primary endpoint was the odds of achieving a platelet count $\geq 50 \times 10^9/L$
581 and $\leq 400 \times 10^9/L$ for patients receiving PROMACTA relative to placebo and was based on
582 patient response profiles throughout the 6-month treatment period.

583 The median age of the patients treated with PROMACTA and placebo was 47 years and
584 52.5 years, respectively. Approximately half of the patients treated with PROMACTA and
585 placebo (47% and 50%, respectively) were receiving concomitant ITP medication
586 (predominantly corticosteroids) at randomization and had baseline platelet counts $\leq 15 \times 10^9/L$
587 (50% and 48%, respectively). A similar percentage of patients treated with PROMACTA and
588 placebo (37% and 34%, respectively) had a prior splenectomy.

589 In 134 patients who completed 26 weeks of treatment, a sustained platelet response (
590 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
591 treatment period in the absence of rescue medication at any time) was achieved by 60% of
592 patients treated with PROMACTA, compared to 10% of patients treated with placebo

593 (splenectomized patients: PROMACTA 51%, placebo 8%; non-splenectomized patients:
 594 PROMACTA 66%, placebo 11%). The proportion of responders in the PROMACTA treatment
 595 group was between 37% and 56% compared to 7% and 19% in the placebo treatment group for
 596 all on-therapy visits. Patients treated with PROMACTA were significantly more likely to
 597 achieve a platelet count between $50 \times 10^9/L$ and $400 \times 10^9/L$ during the entire 6-month treatment
 598 period compared to those patients treated with placebo.
 599

600 Outcomes of treatment are presented in Table 5 for all patients enrolled in the study.
 601

602 **Table 5. Outcomes of Treatment from the Study 3**

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 (%) ^a	24 (18)	25 (40)

603
 604 Among 94 patients receiving other ITP therapy at baseline, 37 (59%) of 63 patients in the
 605 PROMACTA group and 10 (32%) of 31 patients in the placebo group discontinued concomitant
 606 therapy at some time during the study.

607 **14.3 Extension Study**

608 Patients who completed any prior clinical study with PROMACTA were enrolled in an
 609 open-label, single-arm study in which attempts were made to decrease the dose or eliminate the
 610 need for any concomitant ITP medications. PROMACTA was administered to 299 patients; 249
 611 completed 6 months, 210 patients completed 12 months, and 138 patients completed 24 months
 612 of therapy. The median baseline platelet count was $18 \times 10^9/L$ prior to administration of
 613 PROMACTA.

614 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

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

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

623 **17 PATIENT COUNSELING INFORMATION**

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

625 **17.1 Information for Patients**

626 Prior to treatment, patients should fully understand the risks and benefits of
627 PROMACTA. Inform patients that the risks associated with long-term administration of
628 PROMACTA are unknown and that they must enroll in PROMACTA CARES, which provides
629 for the proper use of PROMACTA in ITP patients.

630 Inform patients of the following risks and considerations for PROMACTA:

- 631 • Therapy with PROMACTA is administered to achieve and maintain a platelet count $\geq 50 \times$
632 $10^9/L$ as necessary to reduce the risk for bleeding; PROMACTA is not used to normalize
633 platelet counts.
- 634 • Therapy with PROMACTA may be associated with hepatobiliary laboratory abnormalities.
635 Monitor serum liver tests (ALT, AST, and bilirubin) prior to initiation of PROMACTA,
636 every 2 weeks during the dose adjustment phase, and monthly following establishment of a
637 stable dose. If bilirubin is elevated, perform fractionation.
- 638 • Inform patients that they should report any of the following signs and symptoms of liver
639 problems to their healthcare provider right away.
 - 640 • yellowing of the skin or the whites of the eyes (jaundice),
 - 641 • unusual darkening of the urine,
 - 642 • unusual tiredness,
 - 643 • right upper stomach area pain.
- 644 • Following discontinuation of PROMACTA, thrombocytopenia and risk of bleeding may
645 reoccur, particularly if PROMACTA is discontinued while the patient is on anticoagulants or
646 antiplatelet agents.
- 647 • Therapy with PROMACTA increases the risk of reticulin fiber formation within the bone
648 marrow, and further fiber formation may progress to marrow fibrosis. Detection of peripheral
649 blood cell abnormalities may necessitate a bone marrow examination.
- 650 • Too much PROMACTA may result in excessive platelet counts and a risk for
651 thrombotic/thromboembolic complications.
- 652 • PROMACTA stimulates certain bone marrow cells to make platelets and may increase the
653 risk for progression of underlying MDS or hematological malignancies.
- 654 • Platelet counts and CBCs, including peripheral blood smears, must be performed weekly
655 until a stable dose of PROMACTA has been achieved; thereafter, platelet counts and CBCs,
656 including peripheral blood smears, must be performed monthly while taking PROMACTA.
- 657 • Patients must be closely monitored with weekly platelet counts and CBCs for at least
658 4 weeks following discontinuation of PROMACTA.
- 659 • Even during therapy with PROMACTA, patients should continue to avoid situations or
660 medications that may increase the risk for bleeding.
- 661 • Patients must be advised to keep at least a 4-hour interval between PROMACTA and foods,
662 mineral supplements, and antacids which contain polyvalent cations such as iron, calcium,
663 aluminum, magnesium, selenium, and zinc.

664

665 PROMACTA is a registered trademark of GlaxoSmithKline.
666



667
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MEDICATION GUIDE

PROMACTA[®] (pro-MAC-ta) (eltrombopag) Tablets

Read this Medication Guide before you start taking PROMACTA and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about PROMACTA?

PROMACTA can cause serious side effects, including:

- **Liver problems.** PROMACTA may damage your liver and cause serious illness and death. You must have blood tests to check your liver before you start taking PROMACTA and during treatment with PROMACTA. Your healthcare provider will order these blood tests. In some cases PROMACTA treatment may need to be stopped. Tell your healthcare provider right away if you have any of these signs and symptoms of liver problems:
 - yellowing of the skin or the whites of the eyes (jaundice)
 - unusual darkening of the urine
 - unusual tiredness
 - right upper stomach area pain
- **Bone marrow changes (increased reticulin and possible bone marrow fibrosis).** Long-term use of PROMACTA may cause changes in your bone marrow. These changes may lead to abnormal blood cells or your body making less blood cells. The mild form of these bone marrow changes is called “increased reticulin” which may progress to a more severe form called “fibrosis”. The mild form may cause no problems while the severe form may cause life-threatening blood problems. Signs of bone marrow changes may show up as abnormal results in your blood tests. Your healthcare provider will decide if abnormal blood test results mean that you should have bone marrow tests or if you should stop taking PROMACTA.
- **Recurrence of low blood platelet count (thrombocytopenia) and risk of bleeding shortly after stopping PROMACTA.** When you stop taking PROMACTA, your blood platelet count may return to a similar low platelet count as before you started taking PROMACTA. These effects are

41 most likely to happen within 4 weeks after you stop taking PROMACTA.
42 The recurrence of low platelet counts may increase your risk of bleeding,
43 especially if you take a blood thinner or other medicines that affect
44 platelets. Your healthcare provider will check your blood platelet counts
45 for at least 4 weeks after you stop taking PROMACTA. Call your
46 healthcare provider right away to report any bruising or bleeding.

47 • **High platelet counts and higher chance for blood clots.** Your chance
48 of getting a blood clot is increased if your platelet count is too high during
49 treatment with PROMACTA. Your chance of getting a blood clot may also
50 be increased during treatment with PROMACTA if you have normal or low
51 platelet counts. You may have severe complications or die from some
52 forms of blood clots, such as clots that travel to the lungs or that cause
53 heart attacks or strokes. Your healthcare provider will check your blood
54 platelet counts, and change your dose or stop PROMACTA if your platelet
55 counts get too high. Tell your healthcare provider right away if you have
56 signs and symptoms of a blood clot in the leg, such as swelling, pain, or
57 tenderness in your leg.

58 Patients with chronic liver disease may be at risk for a type of blood clot
59 in the stomach area. Stomach area pain may be a symptom of this type
60 of blood clot.

61 • **Worsening of blood cancers.** PROMACTA is not for use in patients with
62 blood cancer or a precancerous condition called myelodysplastic
63 syndrome (MDS). If you have one of these conditions, PROMACTA may
64 worsen your cancer or condition and may cause you to die sooner.

65 • **New or worsened cataracts (a clouding of the lens in the eye).**
66 New or worsened cataracts have happened in people taking PROMACTA.
67 Your healthcare provider will check your eyes before and during your
68 treatment with PROMACTA. Tell your healthcare provider about any
69 changes in your eyesight while taking PROMACTA.

70

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

74

75 PROMACTA is available only through a program called "PROMACTA CARES".
76 To receive PROMACTA, you must talk to your healthcare provider,
77 understand the benefits and risks of PROMACTA and agree to enroll into
78 PROMACTA CARES.

79 • During therapy with PROMACTA, your healthcare provider may change
80 your dose of PROMACTA, depending upon the change in your blood

81 platelet count. You must have blood platelet count tests done before,
82 during and after your therapy with PROMACTA.

83

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

86

87 **What is PROMACTA?**

88 PROMACTA is a prescription medicine used to treat low blood platelet counts
89 in adults with chronic immune (idiopathic) thrombocytopenic purpura (ITP),
90 when other medicines to treat your ITP or surgery to remove the spleen
91 have not worked well enough.

92

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

96

97 **PROMACTA is only:**

- 98 • prescribed by healthcare providers who are enrolled in PROMACTA
99 *CARES*.
- 100 • given to people who are enrolled in PROMACTA *CARES*.

101

102 It is not known if PROMACTA works or if it is safe in people under the age of
103 18 years.

104

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

108

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

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

- 111 • have liver or kidney problems
- 112 • have or had a blood clot
- 113 • have a history of cataracts
- 114 • have had surgery to remove your spleen (splenectomy)
- 115 • have a bone marrow problem, including a blood cancer or Myelodysplastic
116 Syndrome (MDS)
- 117 • have bleeding problems
- 118 • are Asian and you are of Chinese, Japanese, Taiwanese, or Korean
119 ancestry, you may need a lower dose of PROMACTA.
- 120 • have any other medical conditions

- 121 • are pregnant, think you may be pregnant, or plan to get pregnant. It is
122 not known if PROMACTA will harm an unborn baby.
- 123 **Pregnancy Registry:** There is a registry for women who become
124 pregnant during treatment with PROMACTA. If you become pregnant,
125 consider this registry. The purpose of the registry is to collect safety
126 information about the health of you and your baby. Contact the registry
127 as soon as you become aware of the pregnancy, or ask your healthcare
128 provider to contact the registry for you. You and your healthcare provider
129 can get information and enroll in the registry by calling 1-888-825-5249.
- 130 • are breast-feeding or plan to breast-feed. It is not known if PROMACTA
131 passes into your breast milk. You and your healthcare provider should
132 decide whether you will take PROMACTA or breast-feed. You should not
133 do both.

134

135 **Tell your healthcare provider about all the medicines you take,**
136 including prescription and non-prescription medicines, vitamins, and herbal
137 products. PROMACTA may affect the way certain medicines work. Certain
138 other medicines may affect the way PROMACTA works.

139

140 Especially tell your healthcare provider if you take:

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

143

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

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

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

152

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

155

156 **How should I take PROMACTA?**

157 To receive PROMACTA, you must first talk with your healthcare provider and
158 understand the benefits and risks of PROMACTA. You must agree to and
159 follow all of the instructions in PROMACTA *CARES*.

160

- 161 • Before you can begin to receive PROMACTA, your healthcare provider will:
 - 162 • explain PROMACTA CARES to you.
 - 163 • answer all of your questions about PROMACTA and PROMACTA CARES.
 - 164 • make sure you read this PROMACTA Medication Guide.
 - 165 • have you sign the PROMACTA CARES Patient Enrollment Form.
- 166 • Take PROMACTA exactly as your healthcare provider tells you. Do not
167 stop using PROMACTA without talking with your healthcare provider first.
168 Do not change your dose or schedule for taking PROMACTA unless your
169 healthcare provider tells you to change it.
- 170 • Take PROMACTA on an empty stomach, either 1 hour before or 2 hours
171 after eating food.
- 172 • Take PROMACTA at least 4 hours before or 4 hours after eating dairy
173 products and calcium fortified juices.
- 174 • If you miss a dose of PROMACTA, wait and take your next scheduled
175 dose. Do not take more than one dose of PROMACTA in one day.
- 176 • If you take too much PROMACTA, you may have a higher chance of
177 serious side effects. Call your healthcare provider right away.
- 178 • Your healthcare provider will check your platelet count every week and
179 change your dose of PROMACTA as needed. This will happen every week
180 until your healthcare provider decides that your dose of PROMACTA can
181 stay the same. After that, you will need to have blood tests every month.
182 When you stop taking PROMACTA, you will need to have blood tests for at
183 least 4 weeks to check if your platelet count drops too low.
- 184 • Tell your healthcare provider about any bruising or bleeding that happens
185 while you take and after you stop taking PROMACTA.

186

187 **What should I avoid while taking PROMACTA?**

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

189

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

191 PROMACTA may cause serious side effects.

192

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

195

196 The most common side effects of PROMACTA are:

- 197 • nausea
- 198 • diarrhea
- 199 • upper respiratory tract infection; symptoms may include runny nose,
200 stuffy nose, and sneezing

- 201 • vomiting
- 202 • muscle aches
- 203 • urinary tract infections; symptoms may include frequent or urgent need
- 204 to urinate, low fever in some patients, pain or burning with urination
- 205 • pain or swelling (inflammation) in your throat or mouth (oropharyngeal
- 206 pain and pharyngitis)
- 207 • abnormal liver function tests
- 208 • abnormal skin sensations such as tingling, itching, or burning
- 209 • back pain
- 210 • 'flu' symptoms (influenza); symptoms may include fever, headache,
- 211 tiredness, cough, sore throat, and body aches
- 212 • rash

213

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

217

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

220

221 **How should I store PROMACTA Tablets?**

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

224

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

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

230

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

235

236 For more information, go to www.PROMACTA.com or call toll-free 1-888-
237 825-5249.

238

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

240 Active Ingredient: eltrombopag olamine.

241 Inactive Ingredients:

- 242 • Tablet Core: Magnesium stearate, mannitol, microcrystalline cellulose,
243 povidone, and sodium starch glycolate.
- 244 • Coating: Hypromellose, polyethylene glycol 400, titanium dioxide, and
245 FD&C Yellow No. 6 aluminum lake (25 mg tablet), FD&C Blue No. 2
246 aluminum lake (50 mg tablet), or Iron Oxide Red and Iron Oxide Black
247 (75 mg tablet).

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249 PROMACTA is a registered trademark of GlaxoSmithKline.

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

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