

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
PROMACTA (eltrombopag) for oral suspension
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

Indications and Usage, Treatment of Thrombocytopenia in Patients with Chronic ITP (1.1)	08/2015
Indications and Usage, Treatment of Severe Aplastic Anemia (1.3)	08/2014
Dosage and Administration, Chronic Immune (Idiopathic) Thrombocytopenia (2.1)	08/2015
Dosage and Administration, Severe Aplastic Anemia (2.3)	08/2014
Dosage and Administration, Administration (2.4)	08/2015

INDICATIONS AND USAGE

PROMACTA is a thrombopoietin receptor agonist indicated for the treatment of:

- thrombocytopenia in adult and pediatric patients 1 year and older with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. (1.1)
- thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. (1.2)
- patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy. (1.3)

Limitations of Use:

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

DOSAGE AND ADMINISTRATION

- Take on an empty stomach (1 hour before or 2 hours after a meal). (2.4)
- **Chronic ITP:** Initiate PROMACTA at 50 mg once daily for most adult and pediatric patients 6 years and older and at 25 mg once daily for pediatric patients aged 1 to 5 years. Dose reductions are needed for patients with hepatic impairment and some patients of East Asian ancestry. Adjust to maintain platelet count greater than or equal to $50 \times 10^9/L$. Do not exceed 75 mg per day. (2.1, 8.6, 8.8)

- **Chronic Hepatitis C-associated Thrombocytopenia:** Initiate PROMACTA at 25 mg once daily for all patients. Adjust to achieve target platelet count required to initiate antiviral therapy. Do not exceed a daily dose of 100 mg. (2.2)
- **Severe Aplastic Anemia:** Initiate PROMACTA at 50 mg once daily for most patients. Reduce initial dose in patients with hepatic impairment or patients of East Asian ancestry. Adjust to maintain platelet count greater than $50 \times 10^9/L$. Do not exceed 150 mg per day. (2.3, 8.6, 8.8)

DOSAGE FORMS AND STRENGTHS

- Tablets: 12.5 mg, 25 mg, 50 mg, 75 mg, and 100 mg (3)
- For oral suspension: 25 mg (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- 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

- In adult patients with ITP, the most common adverse reactions (greater than or equal to 5% and greater than placebo) were: nausea, diarrhea, upper respiratory tract infection, vomiting, increased ALT, myalgia, and urinary tract infection. (6.1)
- In pediatric patients age 1 year and older with ITP, the most common adverse reactions (greater than or equal to 10% and greater than placebo) were upper respiratory tract infection, and nasopharyngitis. (6.1)
- In patients with chronic hepatitis C-associated thrombocytopenia, the most common adverse reactions (greater than or equal to 10% and greater than placebo) were: anemia, pyrexia, fatigue, headache, nausea, diarrhea, decreased appetite, influenza-like illness, asthenia, insomnia, cough, pruritus, chills, myalgia, alopecia, and peripheral edema. (6.1)
- In patients with severe aplastic anemia, the most common adverse reactions (greater than or equal to 20%) were: nausea, fatigue, cough, diarrhea, and headache. (6.1)

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

DRUG INTERACTIONS

Take PROMACTA at least 2 hours before or 4 hours after any medications or products containing polyvalent cations such as antacids, calcium-rich foods, and mineral supplements. (2.4, 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)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2015

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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[®] 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 adult and pediatric patients 1 year and older with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

1.2 Treatment of Thrombocytopenia in Patients with Hepatitis C Infection

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

1.3 Treatment of Severe Aplastic Anemia

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

1.4 Limitations of Use

- PROMACTA should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding.
- PROMACTA should be used only in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy.
- Safety and efficacy have not been established in combination with direct-acting antiviral agents used without interferon for treatment of chronic hepatitis C infection.

2 DOSAGE AND ADMINISTRATION

2.1 Chronic Immune (Idiopathic) Thrombocytopenia

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

Initial Dose Regimen: Adult and Pediatric Patients 6 Years and Older with ITP: Initiate PROMACTA at a dose of 50 mg once daily, except in patients who are of East Asian

35 | ancestry (such as Chinese, Japanese, Taiwanese, or Korean) or who have mild to severe hepatic
36 | impairment (Child-Pugh Class A, B, C).

37 | For patients of East Asian ancestry with ITP, initiate PROMACTA at a reduced dose of
38 | 25 mg once daily [*see Use in Specific Populations (8.8), Clinical Pharmacology (12.3)*].

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

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

45 | ***Pediatric Patients with ITP Aged 1 to 5 Years:*** Initiate PROMACTA at a dose of
46 | 25 mg once daily [*see Use in Specific Populations (8.8), Clinical Pharmacology (12.3)*].

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

54 | When switching between the oral suspension and tablet, assess platelet counts weekly for
55 | 2 weeks, and then follow standard monthly monitoring.

56 |

57 **Table 1. Dose Adjustments of PROMACTA in Patients with Chronic Immune (Idiopathic)**
 58 **Thrombocytopenia**

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. For patients taking 12.5 mg once daily, increase the dose to 25 mg daily before increasing the dose amount by 25 mg.
≥200 x 10 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. For patients taking 25 mg once daily, decrease the dose to 12.5 mg once daily.
>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. For patients taking 25 mg once daily, reinstitute therapy at a daily dose of 12.5 mg.
>400 x 10 ⁹ /L after 2 weeks of therapy at lowest dose of PROMACTA	Discontinue PROMACTA.

59
 60 In patients with ITP and hepatic impairment (Child-Pugh Class A, B, C), after initiating
 61 PROMACTA or after any subsequent dosing increase, wait 3 weeks before increasing the dose.
 62 Modify the dosage regimen of concomitant ITP medications, as medically appropriate, to
 63 avoid excessive increases in platelet counts during therapy with PROMACTA. Do not administer
 64 more than one dose of PROMACTA within any 24-hour period.

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

71 **2.2 Chronic Hepatitis C-associated Thrombocytopenia**

72 Use the lowest dose of PROMACTA to achieve and maintain a platelet count necessary
 73 to initiate and maintain antiviral therapy with pegylated interferon and ribavirin. Dose
 74 adjustments are based upon the platelet count response. Do not use PROMACTA to normalize

75 platelet counts [see *Warnings and Precautions (5.3)*]. In clinical trials, platelet counts generally
76 began to rise within the first week of treatment with PROMACTA [see *Clinical Studies (14.2)*].

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

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

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

86 For specific dosage instructions for peginterferon or ribavirin, refer to their respective
87 prescribing information.

88

89 **Table 2. Dose Adjustments of PROMACTA in Adults with Thrombocytopenia due to**
90 **Chronic Hepatitis C**

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 100 mg/day.
≥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. For patients taking 25 mg once daily, reinstitute therapy at a daily dose of 12.5 mg.
>400 x 10 ⁹ /L after 2 weeks of therapy at lowest dose of PROMACTA	Discontinue PROMACTA.

91
92 **Discontinuation:** The prescribing information for pegylated interferon and ribavirin
93 include recommendations for antiviral treatment discontinuation for treatment futility. Refer to
94 pegylated interferon and ribavirin prescribing information for discontinuation recommendations
95 for antiviral treatment futility.

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

2.3 Severe Aplastic Anemia

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

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

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

Monitoring and Dose Adjustment: Adjust the dose of PROMACTA in 50-mg increments every 2 weeks as necessary to achieve the target platelet count greater than or equal to $50 \times 10^9/L$ as necessary. Do not exceed a dose of 150 mg daily. Monitor clinical hematology and liver tests regularly throughout therapy with PROMACTA and modify the dosage regimen of PROMACTA based on platelet counts as outlined in Table 3.

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

Platelet Count Result	Dose Adjustment or Response
$<50 \times 10^9/L$ following at least 2 weeks of PROMACTA	Increase daily dose by 50 mg to a maximum of 150 mg/day. For patients taking 25 mg once daily, increase the dose to 50 mg daily before increasing the dose amount by 50 mg.
$\geq 200 \times 10^9/L$ to $\leq 400 \times 10^9/L$ at any time	Decrease the daily dose by 50 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
$>400 \times 10^9/L$	Stop PROMACTA for 1 week. Once the platelet count is $<150 \times 10^9/L$, reinstitute therapy at a dose reduced by 50 mg.
$>400 \times 10^9/L$ after 2 weeks of therapy at lowest dose of PROMACTA	Discontinue PROMACTA.

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

Discontinuation: If no hematologic response has occurred after 16 weeks of therapy with PROMACTA, discontinue therapy. If new cytogenetic abnormalities are observed, consider discontinuation of PROMACTA [see *Adverse Reactions (6.1)*]. Excessive platelet count

126 responses (as outlined in Table 3) or important liver test abnormalities also necessitate
127 discontinuation of PROMACTA [see *Warnings and Precautions (5.2)*].

128 **2.4 Administration**

129 Preparation of the Oral Suspension: Prior to use of the oral suspension, ensure
130 patients or caregivers receive training on proper dosing, preparation, and administration of
131 PROMACTA for oral suspension.

132 Administer the oral suspension immediately after preparation. **Discard any suspension**
133 **not administered within 30 minutes after preparation.**

134 Prepare the suspension with water only. NOTE: Do not use hot water to prepare the
135 suspension.

136 For details on preparation and administration of the suspension, see **Instructions for Use.**

137 Administration of Tablets and Oral Suspension: Take PROMACTA on an empty
138 stomach (1 hour before or 2 hours after a meal) [see *Clinical Pharmacology (12.3)*]. Take
139 PROMACTA at least 2 hours before or 4 hours after other medications (e.g., antacids), calcium-
140 rich foods (e.g., dairy products and calcium-fortified juices), or supplements containing
141 polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, and zinc [see *Drug*
142 *Interactions (7.1), Clinical Pharmacology (12.3)*].

143 Do not crush tablets and mix with food or liquids.

144 Prepare the oral suspension with water only.

145 **3 DOSAGE FORMS AND STRENGTHS**

146 **3.1 Tablets**

- 147 • 12.5-mg tablets — round, biconvex, white, film-coated tablets debossed with GS MZ1 and
148 12.5 on one side. Each tablet, for oral administration, contains eltrombopag olamine,
149 equivalent to 12.5 mg of eltrombopag free acid.
- 150 • 25-mg tablets — round, biconvex, orange, film-coated tablets debossed with GS NX3 and
151 25 on one side. Each tablet, for oral administration, contains eltrombopag olamine,
152 equivalent to 25 mg of eltrombopag free acid.
- 153 • 50-mg tablets — round, biconvex, blue, film-coated tablets debossed with GS UFU and
154 50 on one side. Each tablet, for oral administration, contains eltrombopag olamine,
155 equivalent to 50 mg of eltrombopag free acid.
- 156 • 75-mg tablets — round, biconvex, pink, film-coated tablets debossed with GS FFS and 75 on
157 one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to
158 75 mg of eltrombopag free acid.
- 159 • 100-mg tablets — round, biconvex, green, film-coated tablets debossed with GS 1L5. Each
160 tablet, for oral administration, contains eltrombopag olamine, equivalent to 100 mg of
161 eltrombopag free acid.

162 **3.2 For Oral Suspension**

163 25-mg packet — contains a reddish-brown to yellow powder for reconstitution.

164 **4 CONTRAINDICATIONS**

165 None.

166 **5 WARNINGS AND PRECAUTIONS**

167 **5.1 Hepatic Decompensation in Patients with Chronic Hepatitis C**

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

176 **5.2 Hepatotoxicity**

177 PROMACTA can cause liver enzyme elevations [*see Adverse Reactions (6.1)*]. Measure
178 serum ALT, AST, and bilirubin prior to initiation of PROMACTA, every 2 weeks during the
179 dose adjustment phase, and monthly following establishment of a stable dose. PROMACTA
180 inhibits UDP-glucuronosyltransferase (UGT)1A1 and organic anion-transporting polypeptide
181 (OATP)1B1, which may lead to indirect hyperbilirubinemia. If bilirubin is elevated, perform
182 fractionation. Evaluate abnormal serum liver tests with repeat testing within 3 to 5 days. If the
183 abnormalities are confirmed, monitor serum liver tests weekly until resolved or stabilized.
184 Discontinue PROMACTA if ALT levels increase to greater than or equal to 3 x ULN in patients
185 with normal liver function or greater than or equal to 3 x baseline in patients with pre-treatment
186 elevations in transaminases and are:

- 187 • progressively increasing, or
- 188 • persistent for greater than or equal to 4 weeks, or
- 189 • accompanied by increased direct bilirubin, or
- 190 • accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation.

191 If the potential benefit for reinitiating treatment with PROMACTA is considered to
192 outweigh the risk for hepatotoxicity, then consider cautiously reintroducing PROMACTA and
193 measure serum liver tests weekly during the dose adjustment phase. Hepatotoxicity may reoccur
194 if PROMACTA is reinitiated. If liver test abnormalities persist, worsen, or recur, then
195 permanently discontinue PROMACTA.

196 **5.3 Thrombotic/Thromboembolic Complications**

197 In two controlled clinical trials in patients with chronic hepatitis C and
198 thrombocytopenia, 3% (31/955) treated with PROMACTA experienced a thrombotic event
199 compared with 1% (5/484) on placebo. The majority of events were of the portal venous system
200 (1% in patients treated with PROMACTA versus less than 1% for placebo).

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

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

210 In a controlled trial in patients with chronic liver disease and thrombocytopenia not
211 related to ITP undergoing elective invasive procedures (N = 292), the risk of thrombotic events
212 was increased in patients treated with 75 mg of PROMACTA once daily. Seven thrombotic
213 complications (six patients) were reported in the group that received PROMACTA and three
214 thrombotic complications were reported in the placebo group (two patients). All of the
215 thrombotic complications reported in the group that received PROMACTA were portal vein
216 thrombosis (PVT). Symptoms of PVT included abdominal pain, nausea, vomiting, and diarrhea.
217 Five of the six patients in the group that received PROMACTA experienced a thrombotic
218 complication within 30 days of completing treatment with PROMACTA and at a platelet count
219 above $200 \times 10^9/L$. The risk of portal venous thrombosis was increased in thrombocytopenic
220 patients with chronic liver disease treated with 75 mg of PROMACTA once daily for 2 weeks in
221 preparation for invasive procedures.

222 **5.4 Cataracts**

223 In the three controlled clinical trials in adults with chronic ITP, cataracts developed or
224 worsened in 15 (7%) patients who received 50 mg of PROMACTA daily and 8 (7%) placebo-
225 group patients. In the extension trial, cataracts developed or worsened in 4% of patients who
226 underwent ocular examination prior to therapy with PROMACTA. In the two controlled clinical
227 trials in patients with chronic hepatitis C and thrombocytopenia, cataracts developed or worsened
228 in 8% of patients treated with PROMACTA and 5% of patients treated with placebo.

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

233 **6 ADVERSE REACTIONS**

234 The following serious adverse reactions associated with PROMACTA are described in
235 other sections.

- 236 • Hepatic Decompensation in Patients with Chronic Hepatitis C [see *Warnings and*
237 *Precautions (5.1)*]
- 238 • Hepatotoxicity [see *Warnings and Precautions (5.2)*]
- 239 • Thrombotic/Thromboembolic Complications [see *Warnings and Precautions (5.3)*]

240 • Cataracts [see Warnings and Precautions (5.4)]

241 6.1 Clinical Trials Experience

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

245 Chronic Immune (Idiopathic) Thrombocytopenia: Adults: In clinical trials,
246 hemorrhage was the most common serious adverse reaction and most hemorrhagic reactions
247 followed discontinuation of PROMACTA. Other serious adverse reactions included
248 thrombotic/thromboembolic complications [see Warnings and Precautions (5.3)]. The data
249 described below reflect exposure of PROMACTA to 446 patients with chronic ITP aged 18 to
250 85 years, of whom 65% were female, across the ITP clinical development program including
251 three placebo-controlled trials. PROMACTA was administered to 277 patients for at least
252 6 months and 202 patients for at least 1 year.

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

256
257 **Table 4. Adverse Reactions ($\geq 3\%$) from Three Placebo-controlled Trials in Adults with**
258 **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

259

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

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

268

269 **Table 5. Treatment-related Adverse Reactions (≥3%) from Extension Trial in Adults with**
270 **Chronic Immune (Idiopathic) Thrombocytopenia**

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

271

272 In the three controlled chronic ITP trials, serum liver test abnormalities (predominantly
273 Grade 2 or less in severity) were reported in 11% and 7% of patients for PROMACTA and
274 placebo, respectively. Four patients (1%) treated with PROMACTA and three patients in the
275 placebo group (2%) discontinued treatment due to hepatobiliary laboratory abnormalities. Seven
276 of the patients treated with PROMACTA in the controlled trials with hepatobiliary laboratory
277 abnormalities were re-exposed to PROMACTA in the extension trial. Six of these patients again
278 experienced liver test abnormalities (predominantly Grade 1) resulting in discontinuation of
279 PROMACTA in one patient. In the extension chronic ITP trial, one additional patient had
280 PROMACTA discontinued due to liver test abnormalities (less than or equal to Grade 3).

281 In a placebo-controlled trial of PROMACTA in patients with chronic liver disease and
282 thrombocytopenia not related to ITP, six patients treated with PROMACTA and one patient in
283 the placebo group developed portal vein thromboses [see *Warnings and Precautions (5.3)*].

284 **Pediatric Patients:** The data described below reflect median exposure to PROMACTA
285 of 91 days for 107 pediatric patients (aged 1 to 17 years) with chronic ITP, of whom 53% were
286 female, across the randomized phase of two placebo-controlled trials.

287 Table 6 presents the most common adverse drug reactions (experienced by greater than or
288 equal to 3% of pediatric patients 1 year and older receiving PROMACTA) across the two
289 placebo-controlled trials, with a higher incidence for PROMACTA versus placebo.

290
291
292
293

Table 6. Adverse Reactions ($\geq 3\%$) with a Higher Incidence for PROMACTA versus Placebo from Two Placebo-controlled Trials in Pediatric Patients 1 Year and Older with Chronic Immune (Idiopathic) Thrombocytopenia

Adverse Reaction	PROMACTA n = 107 (%)	Placebo n = 50 (%)
Upper respiratory tract infection	17	6
Nasopharyngitis	12	4
Cough	9	0
Diarrhea	9	2
Pyrexia	9	8
Rhinitis	9	6
Abdominal pain	8	4
Oropharyngeal pain	8	2
Toothache	6	0
ALT increased ^a	6	0
Rash	5	2
AST increased	4	0
Rhinorrhea	4	0

294 ^a Includes adverse reactions or laboratory abnormalities $>3 \times$ ULN.

295
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300

Chronic Hepatitis C-associated Thrombocytopenia: In the two placebo-controlled trials, 955 patients with chronic hepatitis C-associated thrombocytopenia received PROMACTA. Table 7 presents the most common adverse drug reactions (experienced by greater than or equal to 10% of patients receiving PROMACTA compared with placebo).

301 **Table 7. Adverse Reactions ($\geq 10\%$ and Greater than Placebo) from Two Placebo-**
 302 **controlled Trials in Adults with Chronic Hepatitis C**

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

303
 304 In the two controlled clinical trials in patients with chronic hepatitis C,
 305 hyperbilirubinemia was reported in 8% of patients receiving PROMACTA compared with 3%
 306 for placebo. Total bilirubin greater than or equal to 1.5 x ULN was reported in 76% and 50% of
 307 patients receiving PROMACTA and placebo, respectively. ALT or AST greater than or equal to
 308 3 x ULN was reported in 34% and 38% of patients for PROMACTA and placebo, respectively.

309 **Severe Aplastic Anemia:** In the single-arm, open-label trial, 43 patients with severe
 310 aplastic anemia received PROMACTA. Eleven patients (26%) were treated for greater than
 311 6 months and 7 patients (16%) were treated for greater than 1 year. The most common adverse
 312 reactions (greater than or equal to 20%) were nausea, fatigue, cough, diarrhea, and headache.
 313

314 **Table 8. Adverse Reactions (≥10%) from One Open-label Trial in Adults with Severe**
 315 **Aplastic Anemia**

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

316
 317 In this trial, patients had bone marrow aspirates evaluated for cytogenetic abnormalities.
 318 Eight patients had a new cytogenetic abnormality reported on therapy, including 5 patients who
 319 had complex changes in chromosome 7.

320 **6.2 Postmarketing Experience**

321 The following adverse reactions have been identified during post approval use of
 322 PROMACTA. Because these reactions are reported voluntarily from a population of uncertain
 323 size, it is not always possible to reliably estimate the frequency or establish a causal relationship
 324 to drug exposure.

325 Vascular Disorders: Thrombotic microangiopathy with acute renal failure.

326 **7 DRUG INTERACTIONS**

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

331 **7.1 Polyvalent Cations (Chelation)**

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

336 Take PROMACTA at least 2 hours before or 4 hours after any medications or products
337 containing polyvalent cations such as antacids, dairy products, and mineral supplements to avoid
338 significant reduction in absorption of PROMACTA due to chelation [see *Dosage and*
339 *Administration (2.4), Clinical Pharmacology (12.3)*].

340 **7.2 Transporters**

341 Coadministration of PROMACTA with the OATP1B1 and BCRP substrate, rosuvastatin,
342 to healthy adult subjects increased plasma rosuvastatin AUC_{0-∞} by 55% and C_{max} by 103% [see
343 *Clinical Pharmacology (12.3)*].

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

352 **7.3 Protease Inhibitors**

353 HIV Protease Inhibitors: In a drug interaction trial, coadministration of PROMACTA
354 with lopinavir/ritonavir (LPV/RTV) decreased plasma eltrombopag exposure by 17% [see
355 *Clinical Pharmacology (12.3)*]. No dose adjustment is recommended when PROMACTA is
356 coadministered with LPV/RTV. Drug interactions with other HIV protease inhibitors have not
357 been evaluated.

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

362 **7.4 Peginterferon alfa-2a/b Therapy**

363 Coadministration of peginterferon alfa-2a (PEGASYS[®]) or -2b (PEGINTRON[®]) did not
364 affect eltrombopag exposure in two randomized, double-blind, placebo-controlled trials with
365 adult patients with chronic hepatitis C [see *Clinical Pharmacology (12.3)*].

366 **8 USE IN SPECIFIC POPULATIONS**

367 **8.1 Pregnancy**

368 Pregnancy Category C

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

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

379 Eltrombopag was administered orally to pregnant rats at 10, 20, or 60 mg/kg/day (0.8, 2,
380 and 6 times, respectively, the human clinical exposure based on AUC in patients with ITP at
381 75 mg/day and 0.3, 1, and 3 times, respectively, the human clinical exposure based on AUC in
382 patients with chronic hepatitis C at 100 mg/day). Decreased fetal weights (6% to 7%) and a
383 slight increase in the presence of cervical ribs were observed at the highest dose which also
384 caused maternal toxicity. However, no evidence of major structural malformations was observed.

385 Pregnant rabbits were treated with oral eltrombopag doses of 30, 80, or 150 mg/kg/day
386 (0.04, 0.3, and 0.5 times, respectively, the human clinical exposure based on AUC in patients
387 with ITP at 75 mg/day and 0.02, 0.1, and 0.3 times, respectively, the human clinical exposure
388 based on AUC in patients with chronic hepatitis C at 100 mg/day). No evidence of fetotoxicity,
389 embryoletality, or teratogenicity was observed.

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

397 **8.3 Nursing Mothers**

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

402 **8.4 Pediatric Use**

403 The safety and efficacy of PROMACTA in pediatric patients 1 year and older with
404 chronic ITP were evaluated in two double-blind, placebo-controlled trials [*see Adverse Reactions*
405 (6.2), *Clinical Studies (14.2)*]. The pharmacokinetics of eltrombopag have been evaluated in 168
406 pediatric patients 1 year and older with ITP dosed once daily [*see Clinical Pharmacology*
407 (12.3)]. See *Dosage and Administration (2.1)* for dosing recommendations for pediatric patients

408 1 year and older. The safety and efficacy of PROMACTA in pediatric patients younger than
409 1 year with ITP have not yet been established.

410 The safety and efficacy of PROMACTA in pediatric patients with thrombocytopenia
411 associated with chronic hepatitis C and severe aplastic anemia have not been established.

412 **8.5 Geriatric Use**

413 Of the 106 patients in two randomized clinical trials of PROMACTA 50 mg in chronic
414 ITP, 22% were 65 years of age and over, while 9% were 75 years of age and over. In the two
415 randomized clinical trials of PROMACTA in patients with chronic hepatitis C and
416 thrombocytopenia, 7% were 65 years of age and over, while fewer than 1% were 75 years of age
417 and over. No overall differences in safety or effectiveness were observed between these patients
418 and younger patients in the placebo-controlled trials, but greater sensitivity of some older
419 individuals cannot be ruled out.

420 **8.6 Hepatic Impairment**

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

423 Reduce the initial dose of PROMACTA in patients with chronic ITP (adults and pediatric
424 patients 6 years and older only) or severe aplastic anemia who also have hepatic impairment
425 (Child-Pugh Class A, B, C) [*see Dosage and Administration (2.1, 2.3), Warnings and*
426 *Precautions (5.2)*]. No dosage adjustment is necessary for patients with chronic hepatitis C and
427 hepatic impairment [*see Clinical Pharmacology (12.3)*].

428 **8.7 Renal Impairment**

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

432 **8.8 Ethnicity**

433 Patients of East Asian ethnicity (i.e., Japanese, Chinese, Taiwanese, and Korean) exhibit
434 higher eltrombopag exposures. A reduction in the initial dose of PROMACTA is recommended
435 for patients of East Asian ancestry with ITP (adult and pediatric patients 6 years and older only)
436 or severe aplastic anemia [*see Dosage and Administration (2.1, 2.3)*]. No dose reduction is
437 needed in patients of East Asian ethnicity with chronic hepatitis C [*see Clinical Pharmacology*
438 *(12.3)*].

439 **10 OVERDOSAGE**

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

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

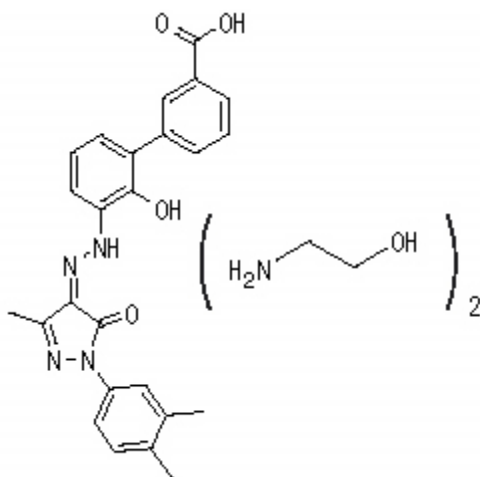
446 dexamethasone, and plasmapheresis; however, the abnormal platelet count and liver test
447 abnormalities persisted for 3 weeks. After 2 months' follow-up, all events had resolved without
448 sequelae.

449 In case of an overdose, consider oral administration of a metal cation-containing
450 preparation, such as calcium, aluminum, or magnesium preparations to chelate eltrombopag and
451 thus limit absorption. Closely monitor platelet counts. Reinitiate treatment with PROMACTA in
452 accordance with dosing and administration recommendations [see *Dosage and Administration*
453 (2.1, 2.2)].

454 11 DESCRIPTION

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

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



465 Eltrombopag olamine is practically insoluble in aqueous buffer across a pH range of 1 to
466 7.4, and is sparingly soluble in water.

468 PROMACTA (eltrombopag) tablets contain eltrombopag olamine in the amount
469 equivalent to 12.5 mg, 25 mg, 50 mg, 75 mg, or 100 mg of eltrombopag free acid. The inactive
470 ingredients of PROMACTA tablets are: **Tablet Core:** magnesium stearate, mannitol,
471 microcrystalline cellulose, povidone, and sodium starch glycolate. **Coating:** hypromellose (12.5-
472 mg, 25-mg, 50-mg, and 75-mg tablets) or polyvinyl alcohol and talc (100-mg tablet),
473 polyethylene glycol 400, titanium dioxide, polysorbate 80 (12.5-mg tablet), FD&C Yellow No. 6
474 aluminum lake (25-mg tablet), FD&C Blue No. 2 aluminum lake (50-mg tablet), Iron Oxide Red

475 and Iron Oxide Black (75-mg tablet), or Iron Oxide Yellow and Iron Oxide Black (100-mg
476 tablet).

477 PROMACTA (eltrombopag) for oral suspension packets contain a reddish-brown to
478 yellow powder which produces a reddish-brown suspension when reconstituted with water. Each
479 25-mg packet delivers eltrombopag olamine equivalent to 25 mg of eltrombopag free acid. The
480 inactive ingredients of PROMACTA for oral suspension are mannitol, sucralose, and xanthan
481 gum.

482 **12 CLINICAL PHARMACOLOGY**

483 **12.1 Mechanism of Action**

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

487 **12.3 Pharmacokinetics**

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

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

496 In a second trial, administration of a single 25-mg dose of eltrombopag for oral
497 suspension to adults with a high-calcium, moderate-fat, moderate-calorie meal reduced plasma
498 eltrombopag $AUC_{0-\infty}$ by 75% (90% CI: 71%, 88%) and C_{max} by 79% (90% CI: 76%, 82%).
499 Administration of a single 25-mg dose of eltrombopag for oral suspension 2 hours after the high-
500 calcium meal reduced plasma eltrombopag $AUC_{0-\infty}$ by 47% (90% CI: 40%, 53%) and C_{max} by
501 48% (90% CI: 40%, 54%). Administration of a single 25-mg dose of eltrombopag for oral
502 suspension 2 hours before the high-calcium meal reduced plasma eltrombopag $AUC_{0-\infty}$ by 20%
503 (90% CI: 9%, 29%) and C_{max} by 14% (90% CI: 2%, 25%).

504 In a relative bioavailability trial in adults, the eltrombopag for oral suspension delivered
505 22% higher plasma $AUC_{0-\infty}$ than the tablet formulation.

506 Distribution: The concentration of eltrombopag in blood cells is approximately 50% to
507 79% of plasma concentrations based on a radiolabel study. *In vitro* studies suggest that
508 eltrombopag is highly bound to human plasma proteins (greater than 99%). Eltrombopag is a
509 substrate of BCRP, but is not a substrate for P-glycoprotein (P-gp) or OATP1B1.

510 Metabolism: Absorbed eltrombopag is extensively metabolized, predominantly through
511 pathways including cleavage, oxidation, and conjugation with glucuronic acid, glutathione, or
512 cysteine. *In vitro* studies suggest that CYP1A2 and CYP2C8 are responsible for the oxidative

513 metabolism of eltrombopag. UGT1A1 and UGT1A3 are responsible for the glucuronidation of
514 eltrombopag.

515 **Elimination:** The predominant route of eltrombopag excretion is via feces (59%), and
516 31% of the dose is found in the urine. Unchanged eltrombopag in feces accounts for
517 approximately 20% of the dose; unchanged eltrombopag is not detectable in urine. The plasma
518 elimination half-life of eltrombopag is approximately 21 to 32 hours in healthy subjects and 26
519 to 35 hours in patients with ITP.

520 **Drug Interactions: Polyvalent Cation-containing Antacids:** In a clinical trial,
521 coadministration of 75 mg of PROMACTA with a polyvalent cation-containing antacid
522 (1,524 mg aluminum hydroxide, 1,425 mg magnesium carbonate, and sodium alginate) to 26
523 healthy adult subjects decreased plasma eltrombopag $AUC_{0-\infty}$ and C_{max} by approximately 70%.
524 The contribution of sodium alginate to this interaction is not known.

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

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

533 **Protease Inhibitors: HIV Protease Inhibitors:** In a clinical trial, coadministration of
534 repeat-dose lopinavir 400 mg/ritonavir 100 mg twice daily with a single dose of PROMACTA
535 100 mg to 40 healthy adult subjects decreased plasma eltrombopag $AUC_{0-\infty}$ by 17%.

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

540 **Pegylated Interferon alfa-2a + Ribavirin and Pegylated Interferon alfa-2b +**
541 **Ribavirin:** The pharmacokinetics of eltrombopag in both the presence and absence of pegylated
542 interferon alfa-2a and -2b therapy were evaluated using a population pharmacokinetic analysis in
543 635 patients with chronic hepatitis C. The population PK model estimates of clearance indicate
544 no significant difference in eltrombopag clearance in the presence of pegylated interferon alfa
545 plus ribavirin therapy.

546 **In vitro Studies:** Eltrombopag is an inhibitor of CYP2C8 and CYP2C9 *in vitro*.
547 Eltrombopag is an inhibitor of UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7,
548 and UGT2B15 *in vitro*. Eltrombopag is an inhibitor of the organic anion transporting polypeptide
549 OATP1B1 and BCRP *in vitro*.

550 **Specific Populations: Ethnicity:** Based on two population PK analyses of eltrombopag
551 concentrations in patients with ITP or chronic hepatitis C, East Asian (i.e., Japanese, Chinese,

552 Taiwanese, Korean) subjects exhibited 50% to 55% higher eltrombopag plasma concentrations
553 compared with non-East Asian subjects [see *Dosage and Administration (2.1, 2.3)*].

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

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

566 **Chronic Liver Disease:** A population PK analysis in thrombocytopenic patients with
567 chronic liver disease following repeat doses of eltrombopag demonstrated that mild hepatic
568 impairment resulted in an 87% to 110% higher plasma eltrombopag $AUC_{(0-\tau)}$ and patients with
569 moderate hepatic impairment had approximately 141% to 240% higher plasma eltrombopag
570 $AUC_{(0-\tau)}$ values compared with patients with normal hepatic function. The half-life of
571 eltrombopag was prolonged 3-fold in patients with mild hepatic impairment and 4-fold in
572 patients with moderate hepatic impairment. This clinical trial did not evaluate protein-binding
573 effects.

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

580 **Renal Impairment:** The disposition of a single 50-mg dose of PROMACTA in patients
581 with mild (creatinine clearance [CrCl] of 50 to 80 mL/min), moderate (CrCl of 30 to
582 49 mL/min), and severe (CrCl less than 30 mL/min) renal impairment was compared with
583 subjects with normal renal function. Average total plasma eltrombopag $AUC_{0-\infty}$ was 32% to 36%
584 lower in subjects with mild to moderate renal impairment and 60% lower in subjects with severe
585 renal impairment compared with healthy subjects. The effect of renal impairment on unbound
586 (active) eltrombopag exposure has not been assessed.

587 **Pediatric Patients:** The pharmacokinetics of eltrombopag have been evaluated in 168
588 pediatric patients 1 year and older with ITP dosed once daily in two trials. Plasma eltrombopag
589 apparent clearance following oral administration (CL/F) increased with increasing body weight.
590 East Asian pediatric patients with ITP had approximately 43% higher plasma eltrombopag
591 $AUC_{(0-\tau)}$ values as compared with non-East Asian patients.

592 Plasma eltrombopag $AUC_{(0-\tau)}$ and C_{max} in pediatric patients aged 12 to 17 years was
 593 similar to that observed in adults. The pharmacokinetic parameters of eltrombopag in pediatric
 594 patients with ITP are shown in Table 9.

595

596 **Table 9. Geometric Mean (95% CI) Steady-state Plasma Eltrombopag Pharmacokinetic**
 597 **Parameters^a in Patients with ITP (Normalized to a Once-daily 50-mg Dose)**

Age	C_{max}^b (mcg/mL)	$AUC_{(0-\tau)}^b$ (mcg.h/mL)
Adults (n = 108)	7.03 (6.44, 7.68)	101 (91.4, 113)
12 to 17 years (n = 62)	6.80 (6.17, 7.50)	103 (91.1, 116)
6 to 11 years (n = 68)	10.3 (9.42, 11.2)	153 (137, 170)
1 to 5 years (n = 38)	11.6 (10.4, 12.9)	162 (139, 187)

598 ^a PK parameters presented as geometric mean (95% CI).

599 ^b Based on population PK post-hoc estimates.

600

601 12.6 Assessment of Risk of QT/QTc Prolongation

602 There is no indication of a QT/QTc prolonging effect of PROMACTA at doses up to
 603 150 mg daily for 5 days. The effects of PROMACTA at doses up to 150 mg daily for 5 days
 604 (supratherapeutic doses) on the QT/QTc interval were evaluated in a double-blind, randomized,
 605 placebo- and positive-controlled (moxifloxacin 400 mg, single oral dose) crossover trial in
 606 healthy adult subjects. Assay sensitivity was confirmed by significant QTc prolongation by
 607 moxifloxacin.

608 13 NONCLINICAL TOXICOLOGY

609 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

616 Eltrombopag was not mutagenic or clastogenic in a bacterial mutation assay or in two *in*
 617 *vivo* assays in rats (micronucleus and unscheduled DNA synthesis, 10 times the human clinical
 618 exposure based on C_{max} in patients with ITP at 75 mg/day and 7 times the human clinical
 619 exposure based on C_{max} in patients with chronic hepatitis C at 100 mg/day). In the *in vitro* mouse

620 lymphoma assay, eltrombopag was marginally positive (less than 3-fold increase in mutation
621 frequency).

622 Eltrombopag did not affect female fertility in rats at doses up to 20 mg/kg/day (2 times
623 the human clinical exposure based on AUC in patients with ITP at 75 mg/day and similar to the
624 human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day).
625 Eltrombopag did not affect male fertility in rats at doses up to 40 mg/kg/day, the highest dose
626 tested (3 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and
627 2 times the human clinical exposure based on AUC in patients with chronic hepatitis C at
628 100 mg/day).

629 **13.2 Animal Pharmacology and/or Toxicology**

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

632 Treatment-related cataracts were detected in rodents in a dose- and time-dependent
633 manner. At greater than or equal to 6 times the human clinical exposure based on AUC in
634 patients with ITP at 75 mg/day and 3 times the human clinical exposure based on AUC in
635 patients with chronic hepatitis C at 100 mg/day, cataracts were observed in mice after 6 weeks
636 and in rats after 28 weeks of dosing. At greater than or equal to 4 times the human clinical
637 exposure based on AUC in patients with ITP at 75 mg/day and 2 times the human clinical
638 exposure based on AUC in patients with chronic hepatitis C at 100 mg/day, cataracts were
639 observed in mice after 13 weeks and in rats after 39 weeks of dosing [*see Warnings and*
640 *Precautions (5.4)*].

641 Renal tubular toxicity was observed in studies up to 14 days in duration in mice and rats
642 at exposures that were generally associated with morbidity and mortality. Tubular toxicity was
643 also observed in a 2-year oral carcinogenicity study in mice at doses of 25, 75, and
644 150 mg/kg/day. The exposure at the lowest dose was 1.2 times the human clinical exposure
645 based on AUC in patients with ITP at 75 mg/day and 0.6 times the human clinical exposure
646 based on AUC in patients with chronic hepatitis C at 100 mg/day. No similar effects were
647 observed in mice after 13 weeks at exposures greater than those associated with renal changes in
648 the 2-year study, suggesting that this effect is both dose- and time-dependent.

649 **14 CLINICAL STUDIES**

650 **14.1 Chronic ITP**

651 Adults: The efficacy and safety of PROMACTA in adult patients with chronic ITP were
652 evaluated in three randomized, double-blind, placebo-controlled trials and in an open-label
653 extension trial.

654 *Trials 1 and 2:* In Trials 1 and 2, patients who had completed at least one prior ITP
655 therapy and who had a platelet count less than $30 \times 10^9/L$ were randomized to receive either
656 PROMACTA or placebo daily for up to 6 weeks, followed by 6 weeks off therapy. During the
657 trials, PROMACTA or placebo was discontinued if the platelet count exceeded $200 \times 10^9/L$.

658 The median age of the patients was 50 years and 60% were female. Approximately 70%
659 of the patients had received at least 2 prior ITP therapies (predominantly corticosteroids,
660 immunoglobulins, rituximab, cytotoxic therapies, danazol, and azathioprine) and 40% of the
661 patients had undergone splenectomy. The median baseline platelet counts (approximately
662 $18 \times 10^9/L$) were similar among all treatment groups.

663 Trial 1 randomized 114 patients (2:1) to PROMACTA 50 mg or placebo. Trial 2
664 randomized 117 patients (1:1:1:1) among placebo or 1 of 3 dose regimens of PROMACTA,
665 30 mg, 50 mg, or 75 mg each administered daily.

666 The efficacy of PROMACTA in this trial was evaluated by response rate, defined as a
667 shift from a baseline platelet count of less than $30 \times 10^9/L$ to greater than or equal to $50 \times 10^9/L$
668 at any time during the treatment period (Table 10).

669

670 **Table 10. Trials 1 and 2 Platelet Count Response ($\geq 50 \times 10^9/L$) Rates in Adults with**
671 **Chronic Immune (Idiopathic) Thrombocytopenia**

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

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

673

674 The platelet count response to PROMACTA was similar among patients who had or had
675 not undergone splenectomy. In general, increases in platelet counts were detected 1 week
676 following initiation of PROMACTA and the maximum response was observed after 2 weeks of
677 therapy. In the placebo and 50-mg-dose groups of PROMACTA, the trial drug was discontinued
678 due to an increase in platelet counts to greater than $200 \times 10^9/L$ in 3% and 27% of the patients,
679 respectively. The median duration of treatment with the 50-mg dose of PROMACTA was
680 42 days in Trial 1 and 43 days in Trial 2.

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

685 **Trial 3:** In this trial, 197 patients were randomized (2:1) to receive either PROMACTA
686 50 mg once daily ($n = 135$) or placebo ($n = 62$) for 6 months, during which time the dose of
687 PROMACTA could be adjusted based on individual platelet counts. Patients were allowed to
688 taper or discontinue concomitant ITP medications after being treated with PROMACTA for
689 6 weeks. Patients were permitted to receive rescue treatments at any time during the trial as
690 clinically indicated.

691 The median ages of the patients treated with PROMACTA and placebo were 47 years
692 and 52.5 years, respectively. Approximately half of the patients treated with PROMACTA and
693 placebo (47% and 50%, respectively) were receiving concomitant ITP medication

694 (predominantly corticosteroids) at randomization and had baseline platelet counts less than or
695 equal to $15 \times 10^9/L$ (50% and 48%, respectively). A similar percentage of patients treated with
696 PROMACTA and placebo (37% and 34%, respectively) had a prior splenectomy.

697 The efficacy of PROMACTA in this trial was evaluated by the odds of achieving a
698 platelet count greater than or equal to $50 \times 10^9/L$ and less than or equal to $400 \times 10^9/L$ for
699 patients receiving PROMACTA relative to placebo and was based on patient response profiles
700 throughout the 6-month treatment period. In 134 patients who completed 26 weeks of treatment,
701 a sustained platelet response (platelet count greater than or equal to $50 \times 10^9/L$ and less than or
702 equal to $400 \times 10^9/L$ for 6 out of the last 8 weeks of the 26-week treatment period in the absence
703 of rescue medication at any time) was achieved by 60% of patients treated with PROMACTA,
704 compared with 10% of patients treated with placebo (splenectomized patients: PROMACTA
705 51%, placebo 8%; non-splenectomized patients: PROMACTA 66%, placebo 11%). The
706 proportion of responders in the group of patients treated with PROMACTA was between 37%
707 and 56% compared with 7% and 19% in the placebo treatment group for all on-therapy visits.
708 Patients treated with PROMACTA were significantly more likely to achieve a platelet count
709 between $50 \times 10^9/L$ and $400 \times 10^9/L$ during the entire 6-month treatment period compared with
710 those patients treated with placebo.

711 Outcomes of treatment are presented in Table 11 for all patients enrolled in the trial.

712
713 **Table 11. Outcomes of Treatment from Trial 3 in Adults with Chronic Immune**
714 **(Idiopathic) 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)

715
716 Among 94 patients receiving other ITP therapy at baseline, 37 (59%) of 63 patients
717 treated with PROMACTA and 10 (32%) of 31 patients in the placebo group discontinued
718 concomitant therapy at some time during the trial.

719 **Extension Trial:** Patients who completed any prior clinical trial with PROMACTA were
720 enrolled in an open-label, single-arm trial in which attempts were made to decrease the dose or
721 eliminate the need for any concomitant ITP medications. PROMACTA was administered to
722 299 patients; 249 completed 6 months, 210 patients completed 12 months, and 138 patients
723 completed 24 months of therapy. The median baseline platelet count was $19 \times 10^9/L$ prior to
724 administration of PROMACTA.

725 **Pediatric Patients:** The efficacy and safety of PROMACTA in pediatric patients 1 year
726 and older with chronic ITP were evaluated in two double-blind, placebo-controlled trials. The
727 trials differed in time since ITP diagnosis: at least 6 months versus at least 12 months. During the
728 trials, doses could be increased every 2 weeks to a maximum of 75 mg once daily. The dose of

729 PROMACTA was reduced if the platelet count exceeded $200 \times 10^9/L$ and interrupted and
730 reduced if it exceeded $400 \times 10^9/L$.

731 *Trial 4:* Patients refractory or relapsed to at least one prior ITP therapy with a platelet
732 count less than $30 \times 10^9/L$ ($n = 92$) were stratified by age and randomized (2:1) to PROMACTA
733 ($n = 63$) or placebo ($n = 29$). The starting dose for patients aged 6 to 17 years was 50 mg once
734 daily for those at least 27 kg and 37.5 mg once daily for those less than 27 kg, administered as
735 oral tablets. A reduced dose of 25 mg once daily was used for East Asian patients aged 6 to
736 17 years regardless of weight. The starting dose for patients aged 1 to 5 years was 1.2 mg/kg
737 once daily (0.8 mg/kg once daily for East Asian patients) administered as oral suspension.

738 The 13-week, randomized, double-blind period was followed by a 24-week, open-label
739 period where patients from both arms were eligible to receive PROMACTA.

740 The median age of the patients was 9 years and 48% were female. Approximately 62% of
741 patients had a baseline platelet count less than or equal to $15 \times 10^9/L$, a characteristic that was
742 similar between treatment arms. The percentage of patients with at least 2 prior ITP therapies
743 (predominantly corticosteroids and immunoglobulins) was 73% in the group treated with
744 PROMACTA and 90% in the group treated with placebo. Four patients in the group treated with
745 PROMACTA had undergone splenectomy.

746 The efficacy of PROMACTA in this trial was evaluated by the proportion of subjects on
747 PROMACTA achieving platelet counts $\geq 50 \times 10^9/L$ (in the absence of rescue therapy) for at least
748 6 out of 8 weeks between Weeks 5 to 12 of the randomized, double-blind period (Table 12).
749

750 **Table 12. Trial 4 Platelet Count Response ($\geq 50 \times 10^9/L$ without Rescue) for 6 out of 8**
751 **Weeks (between Weeks 5 to 12) Overall and by Age Cohort in Pediatric Patients 1 Year**
752 **and Older with Chronic Immune (Idiopathic) Thrombocytopenia**

Age Cohort	PROMACTA	Placebo
Overall	26/63 (41%) ^a	1/29 (3%)
12 to 17 years	10/24 (42%)	1/10 (10%)
6 to 11 years	11/25 (44%)	0/13 (0%)
1 to 5 years	5/14 (36%)	0/6 (0%)

753 ^a *P* value = <0.001 for PROMACTA versus placebo.
754

755 More pediatric patients treated with PROMACTA (75%) compared with placebo (21%)
756 had at least one platelet count greater than or equal to $50 \times 10^9/L$ during the first 12 weeks of
757 randomized treatment in absence of rescue therapy. Fewer pediatric patients treated with
758 PROMACTA required rescue treatment during the randomized, double-blind period compared
759 with placebo-treated patients (19% [12/63] versus 24% [7/29]). In the patients who achieved a
760 platelet response ($\geq 50 \times 10^9/L$ without rescue) for 6 out of 8 weeks (between weeks 5 to 12),
761 62% (16/26) had an initial response in the first 2 weeks after starting PROMACTA.

762 Patients were permitted to reduce or discontinue baseline ITP therapy only during the
763 open-label phase of the trial. Among 15 patients receiving other ITP therapy at baseline, 53%

764 (8/15) reduced (n = 1) or discontinued (n = 7) concomitant therapy, mainly corticosteroids,
765 without needing rescue therapy.

766 **Trial 5:** Patients refractory or relapsed to at least one prior ITP therapy with a platelet
767 count less than $30 \times 10^9/L$ (n = 67) were stratified by age and randomized (2:1) to PROMACTA
768 (n = 45) or placebo (n = 22). The starting dose for patients aged 12 to 17 years was 37.5 mg once
769 daily regardless of weight or race. The starting dose for patients aged 6 to 11 years was 50 mg
770 once daily for those greater than or equal to 27 kg and 25 mg once daily for those less than
771 27 kg, administered as oral tablets. Reduced doses of 25 mg (for those greater than or equal to
772 27 kg) and 12.5 mg (for those less than 27 kg), each once daily, were used for East Asian
773 patients in this age range. The starting dose for patients aged 1 to 5 years was 1.5 mg/kg once
774 daily (0.8 mg/kg once daily for East Asian patients) administered as oral suspension.

775 The 7-week, randomized, double-blind period was followed by an open-label period of
776 up to 24 weeks where patients from both arms were eligible to receive PROMACTA.

777 The median age of the patients was 10 years and 60% were female. Approximately 51%
778 of patients had a baseline platelet count less than or equal to $15 \times 10^9/L$. The percentage of
779 patients with at least 2 prior ITP therapies (predominantly corticosteroids and immunoglobulins)
780 was 84% in the group treated with PROMACTA and 86% in the group treated with placebo.
781 Five patients in the group treated with PROMACTA had undergone splenectomy.

782 The efficacy of PROMACTA in this trial was evaluated by the proportion of patients
783 achieving platelet counts greater than or equal to $50 \times 10^9/L$ (in absence of rescue therapy) at
784 least once between Weeks 1 and 6 of the randomized, double-blind period (Table 13). Platelet
785 response to PROMACTA was consistent across the age cohorts.

786
787 **Table 13. Trial 5 Platelet Count Response ($\geq 50 \times 10^9/L$ without Rescue) Rates in Pediatric**
788 **Patients 1 Year and Older with Chronic Immune (Idiopathic) Thrombocytopenia**

	PROMACTA	Placebo
Overall	28/45 (62%) ^a	7/22 (32%)
12 to 17 years	10/16 (62%)	0/8 (0%)
6 to 11 years	12/19 (63%)	3/9 (33%)
1 to 5 years	6/10 (60%)	4/5 (80%)

789 ^a P value = 0.011 for PROMACTA versus placebo.

790
791 Fewer pediatric patients treated with PROMACTA required rescue treatment during the
792 randomized, double-blind period compared with placebo-treated patients (13% [6/45] versus
793 50% [11/22]).

794 Patients were permitted to reduce or discontinue baseline ITP therapy only during the
795 open-label phase of the trial. Among 13 patients receiving other ITP therapy at baseline, 46%
796 (6/13) reduced (n = 3) or discontinued (n = 3) concomitant therapy, mainly corticosteroids,
797 without needing rescue therapy.

798 **14.2 Chronic Hepatitis C-associated Thrombocytopenia**

799 The efficacy and safety of PROMACTA for the treatment of thrombocytopenia in adult
800 patients with chronic hepatitis C were evaluated in two randomized, double-blind, placebo-
801 controlled trials. Trial 1 utilized peginterferon alfa-2a (PEGASYS[®]) plus ribavirin for antiviral
802 treatment and Trial 2 utilized peginterferon alfa-2b (PEGINTRON[®]) plus ribavirin. In both trials,
803 patients with a platelet count of less than $75 \times 10^9/L$ were enrolled and stratified by platelet
804 count, screening HCV RNA, and HCV genotype. Patients were excluded if they had evidence of
805 decompensated liver disease with Child-Pugh score greater than 6 (class B and C), history of
806 ascites, or hepatic encephalopathy. The median age of the patients in both trials was 52 years,
807 63% were male, and 74% were Caucasian. Sixty-nine percent of patients had HCV genotypes 1,
808 4, 6, with the remainder genotypes 2 and 3. Approximately 30% of patients had been previously
809 treated with interferon and ribavirin. The majority of patients (90%) had bridging fibrosis and
810 cirrhosis, as indicated by noninvasive testing. A similar proportion (95%) of patients in both
811 treatment groups had Child-Pugh Class A (score 5 to 6) at baseline. A similar proportion of
812 patients (2%) in both treatment groups had baseline international normalized ratio (INR) greater
813 than 1.7. Median baseline platelet counts (approximately $60 \times 10^9/L$) were similar in both
814 treatment groups. The trials consisted of 2 phases – a pre-antiviral treatment phase and an
815 antiviral treatment phase. In the pre-antiviral treatment phase, patients received open-label
816 PROMACTA to increase the platelet count to a threshold of greater than or equal to $90 \times 10^9/L$
817 for Trial 1 and greater than or equal to $100 \times 10^9/L$ for Trial 2. PROMACTA was administered at
818 an initial dose of 25 mg once daily for 2 weeks and increased in 25-mg increments over 2- to 3-
819 week periods to achieve the optimal platelet count to initiate antiviral therapy. The maximal time
820 patients could receive open-label PROMACTA was 9 weeks. If threshold platelet counts were
821 achieved, patients were randomized (2:1) to the same dose of PROMACTA at the end of the pre-
822 treatment phase or to placebo. PROMACTA was administered in combination with pegylated
823 interferon and ribavirin per their respective prescribing information for up to 48 weeks.

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

829 In both trials, a significantly greater proportion of patients treated with PROMACTA
830 achieved SVR (see Table 14). The improvement in the proportion of patients who achieved SVR
831 was consistent across subgroups based on baseline platelet count (less than $50 \times 10^9/L$ versus
832 greater than or equal to $50 \times 10^9/L$). In patients with high baseline viral loads (greater than or
833 equal to 800,000), the SVR rate was 18% (82/452) for PROMACTA versus 8% (20/239) for
834 placebo.

835

836 **Table 14. Trials 1 and 2 Sustained Virologic Response in Adults with Chronic Hepatitis C**

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

837 ^a PROMACTA given in combination with peginterferon alfa-2a (180 mcg once weekly for
838 48 weeks for genotypes 1/4/6; 24 weeks for genotype 2 or 3) plus ribavirin (800 to 1,200 mg
839 daily in 2 divided doses orally).

840 ^b PROMACTA given in combination with peginterferon alfa-2b (1.5 mcg/kg once weekly for
841 48 weeks for genotypes 1/4/6; 24 weeks for genotype 2 or 3) plus ribavirin (800 to 1,400 mg
842 daily in 2 divided doses orally).

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

844 ^d *P* value <0.05 for PROMACTA versus placebo.

845

846 The majority of patients treated with PROMACTA (76%) maintained a platelet count
847 greater than or equal to $50 \times 10^9/L$ compared with 19% for placebo. A greater proportion of
848 patients on PROMACTA did not require any antiviral dose reduction as compared with placebo
849 (45% versus 27%).

850 **14.3 Severe Aplastic Anemia**

851 PROMACTA was studied in a single-arm, single-center, open-label trial in 43 patients
852 with severe aplastic anemia who had an insufficient response to at least one prior
853 immunosuppressive therapy and who had a platelet count less than or equal to $30 \times 10^9/L$.
854 PROMACTA was administered at an initial dose of 50 mg once daily for 2 weeks and increased
855 over 2-week periods up to a maximum dose of 150 mg once daily. The efficacy of PROMACTA
856 in the study was evaluated by the hematologic response assessed after 12 weeks of treatment.
857 Hematologic response was defined as meeting 1 or more of the following criteria: 1) platelet
858 count increases to $20 \times 10^9/L$ above baseline, or stable platelet counts with transfusion
859 independence for a minimum of 8 weeks; 2) hemoglobin increase by greater than 1.5 g/dL, or a
860 reduction in greater than or equal to 4 units of RBC transfusions for 8 consecutive weeks; 3)
861 ANC increase of 100% or an ANC increase greater than $0.5 \times 10^9/L$. PROMACTA was
862 discontinued after 16 weeks if no hematologic response was observed. Patients who responded
863 continued therapy in an extension phase of the trial.

864 The treated population had median age of 45 years (range: 17 to 77 years) and 56% were
 865 male. At baseline, the median platelet count was $20 \times 10^9/L$, hemoglobin was 8.4 g/dL, ANC was
 866 $0.58 \times 10^9/L$, and absolute reticulocyte count was $24.3 \times 10^9/L$. Eighty-six percent of patients
 867 were RBC transfusion dependent and 91% were platelet transfusion dependent. The majority of
 868 patients (84%) received at least 2 prior immunosuppressive therapies. Three patients had
 869 cytogenetic abnormalities at baseline.

870 Table 15 presents the efficacy results.

871

872 **Table 15. Hematologic Response in Patients with Severe Aplastic Anemia**

Outcome	PROMACTA N = 43
Response rate ^a , n (%) 95% CI (%)	17 (40) (25, 56)
Median of duration of response in months (95%CI)	NR ^b (3.0, NR ^b)

873 ^a Includes single- and multi-lineage.

874 ^b NR = Not reached due to few events (relapsed).

875

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

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

882 **16 HOW SUPPLIED/STORAGE AND HANDLING**

883 **16.1 Tablets**

- 884 • The 12.5-mg tablets are round, biconvex, white, film-coated tablets debossed with GS MZ1
 885 and 12.5 on one side and are available in bottles of 30: NDC 0007-4643-13.
- 886 • The 25-mg tablets are round, biconvex, orange, film-coated tablets debossed with GS NX3
 887 and 25 on one side and are available in bottles of 30: NDC 0007-4640-13.
- 888 • The 50-mg tablets are round, biconvex, blue, film-coated tablets debossed with GS UFU and
 889 50 on one side and are available in bottles of 30: NDC 0007-4641-13.
- 890 • The 75-mg tablets are round, biconvex, pink, film-coated tablets debossed with GS FFS and
 891 75 on one side and are available in bottles of 30: NDC 0007-4642-13.
- 892 • The 100-mg tablets are round, biconvex, green, film-coated tablets debossed with GS 1L5
 893 and are available in bottles of 30: NDC 0007-4646-13. This product contains a desiccant.

894

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

898 **16.2 For Oral Suspension**

899 The 25-mg for oral suspension is a reddish-brown to yellow powder in unit-dose packets,
900 co-packaged in a kit with a 40-cc reconstitution vessel, an oral dosing syringe, and a threaded
901 closure with syringe-port capability.

902 Each kit (NDC 0007-4515-27) contains 30 packets: NDC 0007-4515-01.

903 Store at room temperature between 20°C and 25°C (68°F to 77°F); excursions permitted
904 to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Following
905 reconstitution, the product should be administered immediately but may be stored for a
906 maximum period of 30 minutes between 20°C and 25°C (68°F to 77°F); excursions permitted to
907 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Throw away (discard)
908 the mixture if not used within 30 minutes.

909 **17 PATIENT COUNSELING INFORMATION**

910 Advise the patient or caregiver to read the FDA-approved patient labeling (Medication
911 Guide and Instructions for Use).

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

- 914 • For patients with chronic ITP, therapy with PROMACTA is administered to achieve and
915 maintain a platelet count greater than or equal to $50 \times 10^9/L$ as necessary to reduce the risk
916 for bleeding.
- 917 • For patients with chronic hepatitis C, therapy with PROMACTA is administered to achieve
918 and maintain a platelet count necessary to initiate and maintain antiviral therapy with
919 pegylated interferon and ribavirin.
- 920 • Therapy with PROMACTA may be associated with hepatobiliary laboratory abnormalities.
- 921 • Advise patients with chronic hepatitis C and cirrhosis that they may be at risk for hepatic
922 decompensation when receiving alfa interferon therapy.
- 923 • Advise patients that they should report any of the following signs and symptoms of liver
924 problems to their healthcare provider right away.
 - 925 • yellowing of the skin or the whites of the eyes (jaundice)
 - 926 • unusual darkening of the urine
 - 927 • unusual tiredness
 - 928 • right upper stomach area pain
 - 929 • confusion
 - 930 • swelling of the stomach area (abdomen)
- 931 • Advise patients that thrombocytopenia and risk of bleeding may reoccur upon discontinuing
932 PROMACTA, particularly if PROMACTA is discontinued while the patient is on
933 anticoagulants or antiplatelet agents.
- 934 • Advise patients that too much PROMACTA may result in excessive platelet counts and a risk
935 for thrombotic/thromboembolic complications.

- 936 • Advise patients that during therapy with PROMACTA, they should continue to avoid
937 situations or medications that may increase the risk for bleeding.
- 938 • Advise patients to have a baseline ocular examination prior to administration of
939 PROMACTA and be monitored for signs and symptoms of cataracts during therapy.
- 940 • Advise patients to take PROMACTA at least 2 hours before or 4 hours after foods, mineral
941 supplements, and antacids which contain polyvalent cations such as iron, calcium, aluminum,
942 magnesium, selenium, and zinc.
- 943 • Prior to use of the oral suspension, ensure patients or caregivers receive training on proper
944 dosing, preparation, and administration.
- 945 • Inform patients or caregivers how many packets to administer to get the full dose.
946

947 PROMACTA is a registered trademark of the GSK group of companies. The following are
948 registered trademarks of their respective owners: PEGASYS/Hoffmann-La Roche Inc.;
949 PEGINTRON/Schering Corporation.
950



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956
957 PRM:XXPI

MEDICATION GUIDE

**PROMACTA® (pro-MAC-ta)
(eltrombopag)
tablets**

**PROMACTA® (pro-MAC-ta)
(eltrombopag)
for oral suspension**

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 (abdomen) 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 adults and children 1 year of age and older with low blood platelet counts due to chronic immune (idiopathic) thrombocytopenia (ITP), when other medicines to treat ITP or surgery to remove the spleen have not worked well enough.

PROMACTA is also used to treat patients with:

- low blood platelet counts due to chronic hepatitis C virus (HCV) infection before and during treatment with interferon.
- severe aplastic anemia (SAA) when other medicines to treat SAA have not worked well enough.

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

PROMACTA is not used to make platelet counts normal.

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

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

It is not known if PROMACTA is safe and effective in children with chronic hepatitis C or severe aplastic anemia or in children younger than 1 year with ITP.

What should I tell my healthcare provider before taking PROMACTA?

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

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

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

Especially tell your healthcare provider if you take:

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

Certain medicines may keep PROMACTA from working correctly. Take PROMACTA at least 2 hours before or 4 hours after taking these products:

- antacid medicine used to treat stomach ulcers or heartburn
- multivitamins or products that contain iron, calcium, aluminum, magnesium, selenium, and zinc which may be found in mineral supplements

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

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

How should I take PROMACTA?

- Take PROMACTA exactly as your healthcare provider tells you to take it. Your healthcare provider will prescribe the dose of PROMACTA tablets or PROMACTA oral suspension that is right for you.
- If your healthcare provider prescribes PROMACTA oral suspension, see “Instructions for Use” that comes with your medicine for instructions on how to prepare and take your dose.
- Do not stop taking PROMACTA without talking with your healthcare provider first. Do not change your dose or schedule for taking PROMACTA unless your healthcare provider tells you to change it.
- Take PROMACTA on an empty stomach, either 1 hour before or 2 hours after eating food.
- Take PROMACTA at least 2 hours before or 4 hours after eating dairy products and calcium-fortified juices.
- **Take PROMACTA tablets whole. Do not crush PROMACTA tablets and mix with food or liquids.**
If you miss a dose of PROMACTA, wait and take your next scheduled dose. Do not take more than one dose of PROMACTA in one day.
- If you take too much PROMACTA, you may have a higher risk of serious side effects. Call your healthcare provider right away.
- Your healthcare provider will check your platelet count during your treatment with PROMACTA and change your dose of PROMACTA as needed.
- Tell your healthcare provider about any bruising or bleeding that happens while you take and after you stop taking PROMACTA.

What should I avoid while taking PROMACTA?

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

What are the possible side effects of PROMACTA?

PROMACTA may cause serious side effects, including:

- See “**What is the most important information I should know about PROMACTA?**”
- **Abnormal liver function tests.** Your healthcare provider will order blood tests to check your liver before you start taking PROMACTA and during your treatment. In some cases treatment with PROMACTA may need to be stopped due to changes in your liver function tests.
- **High platelet counts and higher risk for blood clots.** Your risk of getting a blood clot is increased if your platelet count is too high during treatment with PROMACTA. Your risk of getting a blood clot may also be increased during treatment with PROMACTA if you have normal or low platelet counts. You may have severe problems or die from some forms of blood clots, such as clots that travel to the lungs or that cause heart attacks or strokes. Your healthcare provider will check your blood platelet counts, and change your dose or stop PROMACTA if your platelet counts get too high. Tell your healthcare provider right away if you have signs and symptoms of a blood clot in the leg, such as swelling, pain, or tenderness in your leg.

People with chronic liver disease may be at risk for a type of blood clot in the stomach area. Tell your healthcare provider right away if you have stomach area pain that may be a symptom of this type of blood clot.
- **New or worsened cataracts (a clouding of the lens in the eye).** New or worsened cataracts have happened in people taking PROMACTA. Your healthcare provider will check your eyes before and during your treatment with PROMACTA. Tell your healthcare provider about any changes in your eyesight while taking PROMACTA.

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

- nausea
- diarrhea
- upper respiratory tract infection. Symptoms may include runny nose, stuffy nose, and sneezing
- vomiting
- muscle aches
- urinary tract infection. Symptoms may include frequent or urgent need to urinate, low fever in some people, pain or burning with urination.
- pain or swelling (inflammation) in your throat or mouth (oropharyngeal pain and pharyngitis)
- abnormal liver function tests
- back pain
- "flu"-like symptoms (influenza) including fever, headache, tiredness, cough, sore throat, and body aches
- skin tingling, itching, or burning
- rash

The most common side effects of PROMACTA in children 1 year and older when used to treat chronic ITP are:

- upper respiratory tract infection. Symptoms may include runny nose, stuffy nose, and sneezing.
- pain or swelling (inflammation) in your nose or throat (nasopharyngitis)
- cough
- diarrhea
- fever
- runny, stuffy nose (rhinitis)
- stomach (abdominal) pain
- pain or swelling (inflammation) in your throat or mouth (oropharyngeal pain)
- toothache
- rash
- abnormal liver function tests

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

- low red blood cell count (anemia)
- fever
- tiredness
- headache
- nausea
- diarrhea
- decreased appetite
- "flu"-like symptoms (influenza) including fever, headache, tiredness, cough, sore throat, and body aches
- feeling weak
- trouble sleeping
- cough
- itching
- chills
- muscle aches
- hair loss
- swelling in your ankles, feet, and legs

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

- nausea
- feeling tired
- cough
- diarrhea
- headache
- pain in arms, legs, hands, or feet
- shortness of breath
- fever
- dizziness
- pain in the nose or throat
- abdominal pain
- bruising
- muscle spasms
- abnormal liver function tests
- joint pain
- runny nose

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

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

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

How should I store PROMACTA tablets and oral suspension?

Tablets:

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

For oral suspension:

- Store PROMACTA for oral suspension at room temperature between 68°F to 77°F (20°C to 25°C).
- After mixing, PROMACTA should be taken right away but may be stored for no more than 30 minutes between 68°F to 77°F (20°C to 25°C). Throw away (discard) the mixture if not used within 30 minutes.

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

General information about the safe and effective use of PROMACTA

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

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

For more information about PROMACTA, go to www.PROMACTA.com or call 1-888-825-5249.

What are the ingredients in PROMACTA?

Tablets:

Active ingredient: eltrombopag olamine.

Inactive ingredients:

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

For oral suspension:

Active ingredient: eltrombopag olamine.

Inactive ingredients: mannitol, sucralose, xanthan gum.

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

Revised August 2015


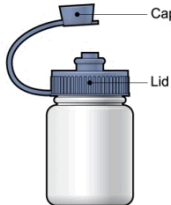
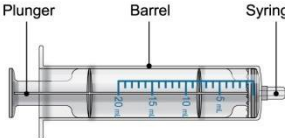
INSTRUCTIONS FOR USE
PROMACTA® (pro-MAC-ta)
(eltrombopag)
for oral suspension

Read all the Instructions for Use and follow the steps below to mix and give a dose of PROMACTA for oral suspension.

Important:

- **Do not take PROMACTA for oral suspension or give it to someone else until you have been shown how to properly give PROMACTA for oral suspension.** Your healthcare provider or nurse will show you how to prepare and give a dose of PROMACTA for oral suspension properly.
- **PROMACTA for oral suspension must be mixed with cool or cold water only.** Do not use hot water to prepare the oral suspension.
- Give the dose of suspension right away after mixing with water. **If medicine is not given within 30 minutes, you will have to mix a new dose.** Throw away (discard) the unused mixture into the trash. Do not pour it down the drain.
- Avoid letting the medicine touch your skin. If this happens, wash the affected area right away with soap and water. Call your doctor if you have a skin reaction or if you have any questions. If you spill any powder or liquid, follow the clean up instructions in **Step 12**.
- Contact your doctor or pharmacist if you have any questions about how to mix or give PROMACTA to the child or if you damage or lose any of the supplies in your kit.
- After you have used all 30 packets, throw all the remaining supplies (mixing bottle, lid with cap, and oral dosing syringe) away in the trash.

Each PROMACTA for oral suspension kit contains the following supplies:

30 packets of PROMACTA for oral suspension	
1 Reusable mixing bottle with lid and cap	
1 Reusable 20-mL oral syringe	

You will need the following to give a single dose of PROMACTA for oral suspension.

From the kit:

- prescribed number of packets
- 1 reusable mixing bottle with lid and cap. NOTE: Due to its small size, the cap may pose a danger of choking to small children.
- 1 reusable 20-mL oral dosing syringe

Not included in the kit:

- 1 clean glass or cup filled with drinking water
- scissors to cut packet
- paper towels or disposable cloth
- gloves (optional)

How do I prepare a dose of PROMACTA for oral suspension?

Step 1. Make sure that the mixing bottle, cap, lid and oral syringe are dry before use. Remove the lid from the mixing bottle.

- Prepare a clean, flat work surface.
- Wash and dry your hands before preparing the medicine.

Step 2. Fill the oral syringe with 20 mL of drinking water from the glass or cup.

- Start with the plunger pushed all the way into the syringe.
- Put the tip of the syringe all the way into the water and pull back on the plunger to the 20 mL mark on the barrel of the syringe.



Step 3. Place the oral syringe into the open mixing bottle. Empty water into open mixing bottle by slowly pushing the plunger all the way into the oral syringe.



Step 4. Take only the prescribed number of packets for one dose out of the kit. You may need to use more than one packet to prepare the entire dose.

- 12.5-mg dose (1 packet) Note: See **Step 9** for instructions on how to give a 12.5-mg dose.
- 25-mg dose (1 packet)
- 50-mg dose (2 packets)
- 75-mg dose (3 packets)

Step 5. Add the prescribed number of packets to the mixing bottle.

- Tap the top of each packet to make sure the contents fall to the bottom.
- Cut off the top of the packet with scissors and empty the entire contents of the packet into the mixing bottle.
- Make sure not to spill the powder outside the mixing bottle.



Step 6. Screw the lid tightly onto the bottle. Make sure the cap is pushed onto the lid.



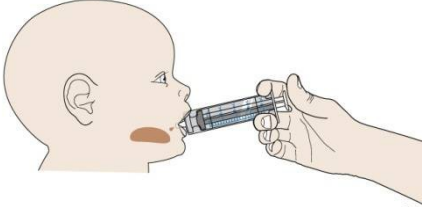
Step 7. Gently and slowly shake the bottle back and forth for at least 20 seconds to mix the water with the powder.

- To prevent the mixture from foaming, do not shake the bottle hard.



How should I give a dose of PROMACTA for oral suspension?

Step 8. Make sure the plunger is pushed all the way into the oral syringe. Pull cap off the mixing bottle lid and insert the syringe tip into the hole in the lid.

<p>Step 9. Transfer the mixture into the oral syringe. The liquid will be dark brown in color.</p> <ul style="list-style-type: none"> • Turn the mixing bottle upside down along with the syringe. • Pull back the plunger: <ul style="list-style-type: none"> ○ to the 10 mL mark on the syringe for a 12.5-mg dose only <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> ○ until all the medicine is in the syringe (25-mg, 50-mg, or 75-mg dose). 	
<p>Step 10. Return the bottle to the upright position and remove the syringe from the bottle.</p>	
<p>Step 11. Giving a dose of PROMACTA for oral suspension to a child.</p> <ul style="list-style-type: none"> • Place the tip of the oral syringe into the inside of the child's cheek. • Slowly push the plunger all the way down to give the entire dose. Make sure the child has time to swallow the medicine. 	
<p>How should I clean up?</p>	
<p>Step 12. Carefully clean up any spill of the powder or suspension with a damp paper towel or disposable cloth.</p> <ul style="list-style-type: none"> • To avoid possibly staining your skin, consider using disposable gloves. • Throw away (discard) used paper towel and gloves in the trash. 	
<p>Step 13. Clean the mixing supplies.</p> <ul style="list-style-type: none"> • Do not reuse any of the mixture remaining in the bottle. • Throw away (discard) any mixture remaining in the mixing bottle in the trash. Do not pour down the drain. • Remove the plunger from the oral syringe. • Rinse the mixing bottle, lid, syringe, and plunger under running water and air dry. The mixing bottle may become stained from the medicine. This is normal. • Wash hands with soap and water. 	

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

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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GlaxoSmithKline

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Issued: August 2015

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