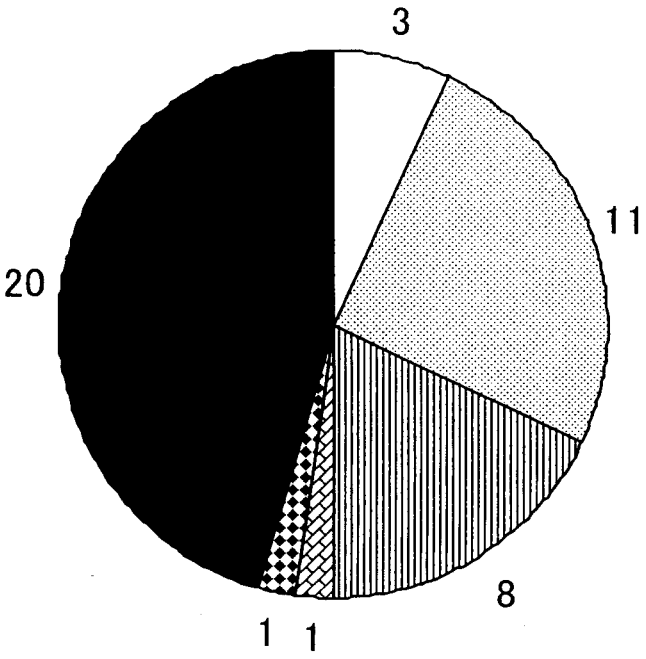
参考資料 6

未承認薬使用問題検討会議での検討状況
（平成17年1月～平成21年2月）

【現在の状況】（平成21年2月末現在）



（検討品目の分類）

抗がん剤	22
先天代謝異常症などの小児用薬	11
その他	11
合計	44

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

PROMACTA* (eltrombopag) Tablets
For oral use
Initial U.S. Approval: 2008

WARNING: RISK FOR HEPATOTOXICITY

See full prescribing information for complete boxed warning

PROMACTA may cause hepatotoxicity:

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

INDICATIONS AND USAGE

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

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

DOSAGE AND ADMINISTRATION

- The starting dose of PROMACTA is 50 mg once daily for most patients; for patients of East Asian ancestry or patients with moderate or severe hepatic insufficiency, the starting dose is 25 mg once daily. (2)
- Give on an empty stomach (1 hour before or 2 hours after a meal). (2)
- Allow a 4-hour interval between PROMACTA and other medications, foods, or supplements containing polyvalent cations (e.g., iron, calcium, aluminum, magnesium, selenium, and zinc). (2, 7.4)
- Adjust the daily dose to achieve and maintain a platelet count ≥50 x 10^9/L in order to reduce the risk for bleeding. (2)
- Do not exceed a daily dose of 75 mg. (2)
- Discontinue PROMACTA if the platelet count does not increase after 4 weeks at the maximum dose; also discontinue PROMACTA for important liver test abnormalities or excessive platelet count responses. (2)

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- PROMACTA may cause hepatotoxicity. Increases in serum aminotransferase levels and bilirubin were observed. Liver chemistries must be measured before the initiation of treatment and regularly during treatment. (5.1)
- Exercise caution when administering to patients with hepatic impairment. (5.1, 8.6)
- PROMACTA is a thrombopoietin receptor agonist and TPO-receptor agonists increase the risk for development or progression of reticulin fiber deposition within the bone marrow. Monitor peripheral blood for signs of marrow fibrosis. (5.2)
- Discontinuation may result in worsened thrombocytopenia than was present prior to therapy. Monitor weekly complete blood counts (CBCs), including platelet counts for at least 4 weeks after discontinuation. (5.3)
- Excessive doses of PROMACTA may increase platelet counts to a level that produces thrombotic/thromboembolic complications. (5.4)
- PROMACTA may increase the risk for hematological malignancies, especially in patients with myelodysplastic syndrome. (5.5)
- Monitor CBCs, including platelet counts and peripheral blood smears, weekly during the dose adjustment phase of therapy with PROMACTA and then monthly following establishment of a stable dose of PROMACTA. (5.6)
- Because of the risk for hepatotoxicity and other risks, PROMACTA is available only through a restricted distribution program. To enroll in the restricted distribution program, PROMACTA *CARES*, call 1-877-9-PROMACTA. (5.8)

ADVERSE REACTIONS

The most common adverse reactions (occurring in more than 1 patient receiving PROMACTA and at a higher rate in PROMACTA versus placebo) were: nausea, vomiting, menorrhagia, myalgia, paresthesia, cataract, dyspepsia, ecchymosis, thrombocytopenia, increased ALT/AST and conjunctival hemorrhage. (6.1)

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm. Enroll pregnant patients in the PROMACTA pregnancy registry by calling 1-888-825-5249. (8.1)
- Nursing Mothers: A decision should be made to discontinue PROMACTA or nursing, taking into account the importance of PROMACTA to the mother. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved MEDICATION GUIDE.

Revised: October 2008
PRM:1PI

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK FOR HEPATOTOXICITY

PROMACTA may cause hepatotoxicity:

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

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

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

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

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

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

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

2.1 Initial Dose Regimen

Initiate PROMACTA at a dose of 50 mg once daily except in patients who are of East Asian ancestry or who have moderate to severe hepatic impairment.

For patients of East Asian ancestry (such as Chinese, Japanese, Taiwanese, or Korean), initiate PROMACTA at a reduced dose of 25 mg once daily *[see Clinical Pharmacology (12.3)]*.

For patients with moderate or severe hepatic impairment, initiate PROMACTA at a reduced dose of 25 mg once daily *[see Use in Specific Populations (8.6)]*.

2.2 Monitoring and Dose Adjustment

After initiating PROMACTA, adjust the dose to achieve and maintain a platelet count ≥50 x 10^9/L as necessary to reduce the risk for bleeding. Do not exceed a dose of 75 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 1. During therapy with PROMACTA, assess CBCs, including platelet count and peripheral blood smears, weekly until a stable platelet count has been achieved. Obtain CBCs including platelet counts and peripheral blood smears, monthly thereafter.

Table 1. Dose Adjustments of PROMACTA

Platelet Count Result	Dose Adjustment or Response
<50 x 10^9/L following at least 2 weeks of PROMACTA	Increase daily dose by 25 mg to a maximum of 75 mg/day.
≥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, reinitiate therapy at a daily dose reduced by 25 mg.
>400 x 10^9/L after 2 weeks of therapy at lowest dose of PROMACTA	Permanently discontinue PROMACTA.

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

2.3 Discontinuation

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

3 DOSAGE FORMS AND STRENGTHS

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

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk for Hepatotoxicity

PROMACTA administration may cause hepatotoxicity. In the controlled clinical studies, one patient experienced Grade 4 (NCI Common Terminology Criteria for Adverse Events [NCI CTCAE] toxicity scale) elevations in serum liver test values during therapy with PROMACTA, worsening of underlying cardiopulmonary disease, and death. No patients in the placebo group

experienced Grade 4 liver test abnormalities. Overall, serum liver test abnormalities (predominantly Grade 2 or less in severity) were reported in 10% and 8% of the PROMACTA and placebo groups, respectively. In the controlled studies, two patients (1%) treated with PROMACTA and two patients in the placebo group (3%) discontinued treatment due to hepatobiliary laboratory abnormalities. Seven of the patients treated with PROMACTA in the controlled studies with hepatobiliary laboratory abnormalities were re-exposed to PROMACTA in the extension study. Six of these patients again experienced liver test abnormalities (predominantly Grade 1) resulting in discontinuation of PROMACTA in one patient. In the extension study, one additional patient had PROMACTA discontinued due to liver test abnormalities (≤Grade 3).

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

- progressive, or
- persistent for ≥4 weeks, or
- accompanied by increased direct bilirubin, or
- accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation.

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

Exercise caution when administering PROMACTA to patients with hepatic disease. Use a lower starting dose of PROMACTA in patients with moderate to severe hepatic disease and monitor closely *[see Dosage and Administration (2.1)]*.

5.2 Bone Marrow Reticulin Formation and Risk for Bone Marrow Fibrosis

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

In the extension study, seven patients had reticulin fiber deposition reported in bone marrow biopsies, including two patients who also had collagen fiber deposition. The fiber deposition was not associated with cytopenias and did not necessitate discontinuation of PROMACTA. However, clinical studies have not excluded a risk of bone marrow fibrosis with cytopenias.

Prior to initiation of PROMACTA, examine the peripheral blood smear closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of PROMACTA, examine peripheral blood smears and CBCs monthly for new or

worsening morphological abnormalities (e.g., teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If the patient develops new or worsening morphological abnormalities or cytopenia(s), discontinue treatment with PROMACTA and consider a bone marrow biopsy, including staining for fibrosis.

5.3 Worsened Thrombocytopenia and Hemorrhage Risk After Cessation of PROMACTA

Discontinuation of PROMACTA may result in thrombocytopenia of greater severity than was present prior to therapy with PROMACTA. This worsened thrombocytopenia may increase the patient's risk of bleeding, particularly if PROMACTA is discontinued while the patient is on anticoagulants or antiplatelet agents. In the controlled clinical studies, transient decreases in platelet counts to levels lower than baseline were observed following discontinuation of treatment in 10% and 6% of the PROMACTA and placebo groups, respectively. Serious hemorrhagic events requiring the use of supportive ITP medications occurred in 3 severely thrombocytopenic patients within one month following the discontinuation of PROMACTA; none were reported among the placebo group.

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

5.4 Thrombotic/Thromboembolic Complications

Thrombotic/thromboembolic complications may result from excessive increases in platelet counts. Excessive doses of PROMACTA or medication errors that result in excessive doses of PROMACTA may increase platelet counts to a level that produces thrombotic/thromboembolic complications. In the controlled clinical studies, one thrombotic/thromboembolic complication was reported within the groups that received PROMACTA and none within the placebo groups. Seven patients experienced thrombotic/thromboembolic complications in the extension study. Use caution when administering PROMACTA to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, etc). To minimize the risk for thrombotic/thromboembolic complications, do not use PROMACTA in an attempt to normalize platelet counts. Follow the dose adjustment guidelines to achieve and maintain a platelet count of $\geq 50 \times 10^9$/L *[see Dosage and Administration (2.2)]*.

5.5 Malignancies and Progression of Malignancies

PROMACTA stimulation of the TPO receptor on the surface of hematopoietic cells may increase the risk for hematologic malignancies. In the controlled clinical studies, patients were treated with PROMACTA for a maximum of 6 weeks and during this period no hematologic malignancies were reported. One hematologic malignancy (non-Hodgkin's lymphoma) was reported in the extension study. PROMACTA is not indicated for the treatment of thrombocytopenia due to causes of thrombocytopenia (e.g., myelodysplasia or chemotherapy) other than chronic ITP.

5.6 Laboratory Monitoring

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

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

5.7 Cataracts

In the controlled clinical studies, cataracts developed or worsened in five (5%) patients who received 50 mg PROMACTA daily and two (3%) placebo-group patients. In the extension study, cataracts developed or worsened in 4% of patients who underwent ocular examination prior to therapy with PROMACTA. Cataracts were observed in toxicology studies of eltrombopag in rodents *[see Nonclinical Toxicology (13.2)]*. Perform a baseline ocular examination prior to administration of PROMACTA and, during therapy with PROMACTA, regularly monitor patients for signs and symptoms of cataracts.

5.8 PROMACTA Distribution Program

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

- Educate patients on the benefits and risks of treatment with PROMACTA, ensure that the patient receives the Medication Guide, instruct them to read it, and encourage them to ask questions when considering PROMACTA. Patients may be educated by the enrolled prescriber or a healthcare provider under that prescriber's direction.
- Review the PROMACTA *CARES* Prescriber Enrollment Forms, sign the form, and return the form according to PROMACTA *CARES* Program instructions.

- As part of the initial prescription process for PROMACTA, obtain the patient's signature on the Patient Enrollment and Consent form, sign it, place the original signed form in the patient's medical record, send a copy to PROMACTA *CARES*, and give a copy to the patient.
- Report any serious adverse events associated with the use of PROMACTA to PROMACTA *CARES* Call Center at 1-877-9-PROMACTA or to the FDA's MedWatch Program at 1-800-FDA-1088.
- Report serious adverse events observed in patients receiving PROMACTA, including events actively solicited at 6-month intervals.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

In clinical studies, hemorrhage was the most common serious adverse reaction and most hemorrhagic reactions followed discontinuation of PROMACTA. Other serious adverse reactions included liver test abnormalities and thrombotic/thromboembolic complications *[see Warnings and Precautions (5.1, 5.2)]*.

The data described below reflect PROMACTA exposure to 313 patients with chronic ITP aged 18 to 85, of whom 65% were female. PROMACTA was studied in 2 randomized, placebo controlled studies in which patients received the drug for no more than 6 weeks. PROMACTA was also studied in an open label single arm study in which patients received the drug over an extended period of time. Overall, PROMACTA was administered to 81 patients for at least 6 months and 39 patients for at least 1 year.

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

Table 2 presents the most common adverse drug reactions (experienced by more than 1 patient receiving PROMACTA) from the placebo-controlled studies, with a higher incidence in PROMACTA versus placebo.

Table 2. Adverse Reactions Identified in Two Placebo-Controlled Studies

Preferred Term	PROMACTA 50mg n = 106 (%)	Placebo n = 67 (%)
Nausea	6	4
Vomiting	4	3
Menorrhagia	4	1
Myalgia	3	1
Paresthesia	3	1
Cataract	3	1
Dyspepsia	2	0
Ecchymosis	2	1
Thrombocytopenia	2	0
Increased ALT	2	0
Increased AST	2	0
Conjunctival hemorrhage	2	1

Among 207 patients with chronic ITP who received PROMACTA in the single-arm extended study, the adverse reactions occurred in a pattern similar to those reported in the placebo-controlled studies.

7 DRUG INTERACTIONS

7.1 Cytochrome P450

In vitro studies demonstrate that CYP1A2 and CYP2C8 are involved in the oxidative metabolism of eltrombopag. The significance of coadministration of PROMACTA with 1) moderate or strong inhibitors of CYP 1A2 (e.g., ciprofloxacin, fluvoxamine) and CYP 2C8 (e.g., gemfibrozil, trimethoprim); 2) inducers of CYP 1A2 (e.g., tobacco, omeprazole) and CYP 2C8 (e.g., rifampin); or 3) other substrates of these CYP enzymes on the systemic exposure of PROMACTA has not been established in clinical studies. Monitor patients for signs and symptoms of excessive eltrombopag exposure when PROMACTA is administered concomitantly with these moderate or strong inhibitors of CYP1A2 or CYP2C8.

7.2 Transporters

In vitro studies demonstrate that eltrombopag is an inhibitor of the organic anion transporting polypeptide OATP1B1 and can increase the systemic exposure of other drugs that are substrates of this transporter (e.g., benzylpenicillin, atorvastatin, fluvastatin, pravastatin, rosuvastatin, methotrexate, nateglinide, repaglinide, rifampin). In a clinical study of healthy adult subjects, administration of a single dose of rosuvastatin following repeated daily PROMACTA dosing increased plasma rosuvastatin $AUC_{0-\infty}$ by 55% and C_{max} by 103% *[see Clinical Pharmacology (12.3)]*.