CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

22291Orig1s012

Trade Name:	**PROMACTA**
Generic or Proper Name:	eltrombopaq
Sponsor:	NOVARTIS PHARMACEUTICALS CORP
Approval Date:	August 26, 2014
Indication:	**PROMACTA** is a thrombopoietin receptor agonist indicated for the treatment of: • thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. • thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. • patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022291/S-012

SUPPLEMENT APPROVAL

GlaxoSmithKline, LLC
Attention: Dennis R. Williams, PharmD
Director, Global Regulatory Affairs
1250 South Collegeville Road
Collegeville, PA 19426

Dear Dr. Williams:

Please refer to your Supplemental New Drug Application (sNDA) dated February 27, 2014, received February 27, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for PROMACTA® (eltrombopag) tablets, 12.5, 25, 50, 75, and 100 mg.

We acknowledge receipt of your amendment dated April 22; June 19; August 8; and August 25, 2014.

This "Prior Approval" supplemental new drug application proposes a new indication for the treatment of cytopenias in patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication

Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eList may be found in the guidance for industry titled *"SPL Standard for Content of Labeling Technical Qs and As"* at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Tinya Sensie, Regulatory Project Manager, at (240) 402-4230.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
08/26/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22291Orig1s012

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

PROMACTA (eltrombopag) tablets, for oral use
Initial U.S. Approval: 2008

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

See full prescribing information for complete boxed warning

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

RECENT MAJOR CHANGES

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

INDICATIONS AND USAGE

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

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

Limitations of Use:

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

DOSAGE AND ADMINISTRATION

- Take on an empty stomach (1 hour before or 2 hours after a meal). (2.4)
- Allow a 4-hour interval between PROMACTA and other medications, foods, or supplements containing polyvalent cations (e.g., iron, calcium, aluminum, magnesium, selenium, and zinc). (2.4)
- **Chronic ITP:** Initiate PROMACTA at 50 mg once daily for most patients. Reduce initial dose in patients with hepatic impairment and/or patients of East Asian ancestry. Adjust to maintain platelet count greater than or equal to 50 x 10^9/L. Do not exceed 75 mg per day. (2.1)
- **Chronic Hepatitis C-associated Thrombocytopenia:** Initiate PROMACTA at 25 mg once daily for all patients. Adjust to achieve target platelet count required to initiate antiviral therapy. Do not exceed a daily dose of 100 mg. (2.2)
- **Severe Aplastic Anemia:** Initiate PROMACTA at 50 mg once daily for most patients. Reduce initial dose in patients with hepatic impairment or patients of East Asian ancestry. Adjust to maintain platelet count greater than 50 x 10^9/L. Do not exceed 150 mg per day. (2.3)

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

None. (4)

WARNINGS and PRECAUTIONS

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

ADVERSE REACTIONS

- The most common adverse reactions in ITP patients (greater than or equal to 3% and greater than placebo) were: nausea, diarrhea, upper respiratory tract infection, vomiting, increased ALT, myalgia, urinary tract infection, oropharyngeal pain, increased AST, pharyngitis, back pain, influenza, paresthesia, and rash. (6.1)
- The most common adverse reactions in thrombocytopenic patients with chronic hepatitis C (greater than or equal to 10% and greater than placebo) were: anemia, pyrexia, fatigue, headache, nausea, diarrhea, decreased appetite, influenza-like illness, asthenia, insomnia, cough, pruritus, chills, myalgia, alopecia, and peripheral edema. (6.1)
- The most common adverse reactions in patients with severe aplastic anemia (greater than or equal to 20%) were: nausea, fatigue, cough, diarrhea, and headache. (6.1)

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

DRUG INTERACTIONS

PROMACTA must not be taken within 4 hours of any medications or products containing polyvalent cations such as antacids, dairy products, and mineral supplements. (7.1)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, PROMACTA may cause fetal harm. (8.1)
- Nursing Mothers: A decision should be made to discontinue PROMACTA or nursing, taking into account the importance of PROMACTA to the mother. (8.3)
- Reduce the initial dose in chronic ITP patients with hepatic impairment. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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 patients with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

1.2 Treatment of Thrombocytopenia in Patients with Hepatitis C Infection

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

1.3 Treatment of Severe Aplastic Anemia

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

1.4 Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Chronic Immune (Idiopathic) Thrombocytopenia

Use the lowest dose of PROMACTA to achieve and maintain a platelet count greater than or equal to 50 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 to normalize platelet counts *[see Warnings and Precautions (5.3)]*. In clinical trials, platelet counts generally increased within 1 to 2 weeks after starting PROMACTA and decreased within 1 to 2 weeks after discontinuing PROMACTA *[see Clinical Studies (14.1)]*.

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

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

For ITP patients 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), Clinical Pharmacology (12.3)]*.

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

Monitoring and Dose Adjustment: After initiating PROMACTA, adjust the dose to achieve and maintain a platelet count greater than or equal to 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 with differentials, including platelet counts, weekly until a stable platelet count has been achieved. Obtain CBCs with differentials, including platelet counts, monthly thereafter.

Table 1. Dose Adjustments of PROMACTA in Adults with Chronic Immune (Idiopathic) 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.
>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. For patients taking 25 mg once daily, reinitiate 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.

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

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.

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 (5.2)]*. Obtain CBCs with differentials, including platelet counts, weekly for at least 4 weeks following discontinuation of PROMACTA.

2.2 Chronic Hepatitis C-associated Thrombocytopenia

Use the lowest dose of PROMACTA to achieve and maintain a platelet count necessary to initiate and maintain antiviral therapy with pegylated interferon and ribavirin. 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 began to rise within the first week of treatment with PROMACTA *[see Clinical Studies (14.2)]*.

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

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

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

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

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

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

PROMACTA should be discontinued when antiviral therapy is discontinued. Excessive platelet count responses, as outlined in Table 2, or important liver test abnormalities also 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 severe aplastic anemia in patients 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 (8.8)(8.6), 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 x 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 x 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.
≥200 x 10^9/L to ≤400 x 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 x 10^9/L	Stop PROMACTA for 1 week. Once the platelet count is <150 x 10^9/L, reinitiate therapy at a dose reduced by 50 mg.
>400 x 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 x 10^9/L, hemoglobin to less than 9 g/dL, or ANC to less than 0.5 x 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 responses (as outlined in Table 3) or important liver test abnormalities also necessitate discontinuation of PROMACTA *[see Warnings and Precautions (5.2)]*.

2.4 Administration

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., dairy products and calcium fortified juices), or supplements containing polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, and zinc *[see Drug Interactions (7.1)]*.

3 DOSAGE FORMS AND STRENGTHS

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

- 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.
- 75 mg tablets — round, biconvex, pink, film-coated tablets debossed with GS FFS and 75 on one side. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to 75 mg of eltrombopag free acid.
- 100 mg tablets — round, biconvex, green, film-coated tablets debossed with GS 1L5. Each tablet, for oral administration, contains eltrombopag olamine, equivalent to 100 mg of eltrombopag free acid.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 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. In two controlled clinical trials in patients with chronic hepatitis C and thrombocytopenia, ascites and encephalopathy occurred more frequently on the arm receiving treatment with PROMACTA plus antivirals (7%) than the placebo plus antivirals arm (4%). Patients with low albumin levels (less than 3.5 g/dL) or Model for End-Stage Liver Disease (MELD) score greater than or equal to10 at baseline had a greater risk for hepatic decompensation on the arm receiving treatment with PROMACTA plus antivirals. Discontinue PROMACTA if antiviral therapy is discontinued.

5.2 Hepatotoxicity

PROMACTA can cause liver enzyme elevations *[see Adverse Reactions (6.1)]*. 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. PROMACTA inhibits UGT1A1 and OATP1B1, which may lead to indirect hyperbilirubinemia. 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 resolved or stabilized. Discontinue PROMACTA if ALT levels increase to greater than or equal to 3X ULN in patients with normal liver function or greater than or equal to 3X baseline in patients with pre-treatment elevations in transaminases and are:

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

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

5.3 Thrombotic/Thromboembolic Complications

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

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

Consider the potential for an increased risk of thromboembolism when administering PROMACTA to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, chronic liver disease). 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 target platelet counts *[see Dosage and Administration (2.1, 2.2, 2.3)]*.

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

5.4 Cataracts

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

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.

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

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

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

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

Table 4. Adverse Reactions (≥3%) from Three Placebo-controlled Trials in Adults with 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

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

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

Table 5. Treatment-related Adverse Reactions (≥3%) from Extension Trial in Adults with 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

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

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

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

Table 6. Adverse Reactions (≥10% and Greater than Placebo) from Two Placebo-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

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

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

Table 7. Adverse Reactions (≥10%) from One Open-label Trial in Adults with Severe 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

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

7 DRUG INTERACTIONS

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

7.1 Polyvalent Cations (Chelation)

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

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

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

7.2 Transporters

Co-administration of PROMACTA with the OATP1B1 and BCRP substrate, rosuvastatin, to healthy adult subjects increased plasma rosuvastatin $AUC_{0-\infty}$ by 55% and C_{max} by 103% *[see Clinical Pharmacology (12.3)]*.

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

7.3 Protease Inhibitors

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

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

7.4 Peginterferon Alfa 2a/b Therapy

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

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

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

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

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

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

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Hepatic Impairment

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

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

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

8.7 Renal Impairment

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

8.8 Ethnicity

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

10 OVERDOSAGE

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

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

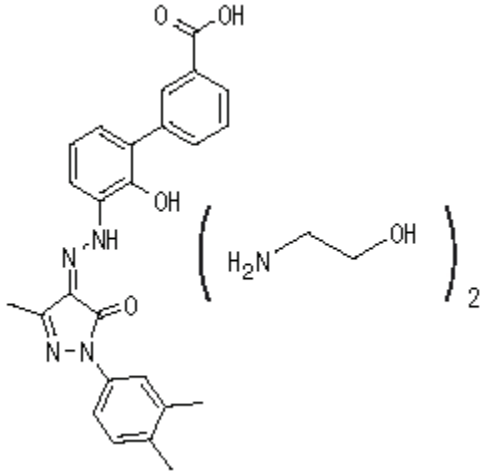
In case of an overdose, consider oral administration of a metal cation-containing preparation, such as calcium, aluminum, or magnesium preparations to chelate eltrombopag and thus limit absorption. Closely monitor platelet counts. Reinitiate treatment with PROMACTA in accordance with dosing and administration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

11 DESCRIPTION

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

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

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



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

The inactive ingredients of PROMACTA are: **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), 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).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

12.6 Assessment of Risk of QT/QTc Prolongation

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

13.2 Animal Pharmacology and/or Toxicology

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

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

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

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

14 CLINICAL STUDIES

14.1 Chronic ITP

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

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

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

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

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

Table 8. Trials 1 and 2 Platelet Count Response (≥50 x 10^9/L) Rates in Adults with 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%)

[a] *P* value <0.001 for PROMACTA versus placebo.

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

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

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

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

The median age of the patients treated with PROMACTA and placebo was 47 years and 52.5 years, respectively. Approximately half of the patients treated with PROMACTA and placebo (47% and 50%, respectively) were receiving concomitant ITP medication (predominantly corticosteroids) at randomization and had baseline platelet counts less than or equal to15 x 10^9/L (50% and 48%, respectively). A similar percentage of patients treated with PROMACTA and placebo (37% and 34%, respectively) had a prior splenectomy.

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

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

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

Outcome	PROMACTA N = 135	Placebo N = 62
Mean number of weeks with platelet counts ≥50 x 10^9/L	11.3	2.4
Requiring rescue therapy, n (%)	24 (18)	25 (40)

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

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

14.2 Chronic Hepatitis C-associated Thrombocytopenia

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

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

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

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

Table 10. Trials 1 and 2 Sustained Virologic Response in Adults with Chronic Hepatitis C

	Trial 1[a]		**Trial 2[b]**	
Pre-antiviral Treatment Phase	**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

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

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

[c] Target platelet count was ≥90 x 10^9/L for Trial 1 and ≥100 x 10^9/L for Trial 2.

[d] *P* value <0.05 for PROMACTA versus placebo.

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

14.3 Severe Aplastic Anemia

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

The treated population had median age of 45 years (range 17 to 77 years) and 56% were male. At baseline, the median platelet count was 20 x 10^9/L, hemoglobin was 8.4 g/dL, ANC was 0.58 x 10^9/L and absolute reticulocyte count was 24.3 x10^9/L. Eighty-six percent of patients were RBC transfusion dependent and 91% were platelet transfusion dependent. The majority of patients (84%) received at least 2 prior immunosuppressive therapies. Three patients had cytogenetic abnormalities at baseline.

Table 11 presents the primary efficacy results.

Table 11. 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])

[a] Includes single and multi-lineage.

[b] NR = not reached due to few events (relapsed).

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

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

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

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

GlaxoSmithKline
Research Triangle Park, NC 27709

PRM:XPI

MEDICATION GUIDE

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

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

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

PROMACTA can cause serious side effects, including:

Liver problems. If you have chronic hepatitis C virus, and take PROMACTA with interferon and ribavirin treatment, PROMACTA may increase your risk of liver problems. Tell your healthcare provider right away if you have any of these signs and symptoms of liver problems:

- yellowing of the skin or the whites of the eyes (jaundice)
- unusual darkening of the urine
- unusual tiredness
- right upper stomach area pain
- confusion
- swelling of the stomach area (abdomen)

See "What are the possible side effects of PROMACTA?" for other side effects of PROMACTA.

What is PROMACTA?

PROMACTA is a prescription medicine used to treat people with:

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

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

PROMACTA is not used to make your platelet count 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.

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 4 hours before or 4 hours after taking these products:

- antacids 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. 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 4 hours before or 4 hours after eating dairy products and calcium fortified juices.
- 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 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 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?

- Store PROMACTA 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.

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?

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).

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

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

GlaxoSmithKline
Research Triangle Park, NC 27709

Revised: August 2014
PRM:XMG

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22291Orig1s012

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	August 20, 2014
From	Kathy M. Robie Suh, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	22-291 S-012
Applicant	GlaxoSmithKline
Date of Submission	February 27, 2014
PDUFA Goal Date	August 27, 2014
Proprietary Name / **Established (USAN) names**	Promacta/ Eltrombopag olamine
Dosage forms / Strength	Oral tablets, (25 mg, 50 mg, 75 mg); proposed new 100 mg tablet
Proposed Indication(s)	"Promacta is a thrombopoietin receptor agonist indicated for the treatment of cytopenias in patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy".
Recommended:	Approval for indication: "Promacta is indicated for the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy".

1. Introduction

Eltrombopag (Promacta) is an orally available small molecule thrombopoietin receptor (TPO-R) agonist approved 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 (accelerated approval, 11/20/2008; converted to full approval 2/25/2011), The approved dose is 50 mg once daily (25 mg in patients of East Asian ancestry or with hepatic impairment) and dose is adjusted to maintain platelet count $\geq 50 \times 10^9$/L but is not to exceed 75 mg daily.
- the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. The approved dose is 25 mg once daily for all patients and dose is adjusted to achieve platelet count required to initiate antiviral therapy, not to exceed 100mg daily. (11/16/2012).

In the current submission the sponsor seeks approval of eltrombopag for treatment of cytopenias in patients with severe aplastic anemia (SAA) who have had an insufficient response to immunosuppressive therapy.

The sponsor was granted Breakthrough Therapy designation for eltrombopag for patients with SAA based on an unmet medical need for therapy for these patients and on published data from an investigator-initiated, single-arm, phase II study in 25 patients with SAA refractory to immunosuppressive therapy. (See review by Dr. A. Dmytrijuk, IND 63293, 1/16/2014) (letter issued 1/27/2014).

Also, eltrombopag has been granted Orphan Product Designation (November 8, 2013) for treatment of aplastic anemia.

To support the proposed indication the sponsor has submitted results of an open-label, single-center, non-randomized, study of eltrombopag in patients with severe aplastic anemia (SAA) and thrombocytopenia (ELT112523) who have had an insufficient response to immunosuppressive therapy. Additional data are provided from an ongoing study in patients with SAA who are receiving standard treatment with hATG/cyclosporine in combination with eltrombopag and from a completed placebo-controlled Phase I/II study in patients with advanced myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).

This supplement has been granted priority review.

2. Background

Severe aplastic anemia (SAA) is a life-threatening, acquired bone marrow failure disease characterized by tri-lineage marrow hypoplasia and a lack of hematopoietic stem and progenitor cells (HSPC) due to an immune-mediated attack on the bone marrow.

The disease is often fatal, due to infection or hemorrhage. Currently used treatments include intensive immunosuppressive therapy (IST) with horse anti-thymocyte globulin and cyclosporine (ATG/CsA), or hematopoietic stem cell transplantation (HSCT), where appropriate and possible. However, about half of patients will either not have an initial response or will relapse.

3. CMC/Device

The Chemistry, Manufacturing and Controls (CMC) Review of this supplemental applicartion was completed by Janice Brown (signed 7/18/2014). The review indicates that the sponsor has requested a categorical exclusion under 21 CFR, part 25, §25.31(b) for eltrombopag olamine and concludes that the exclusion can be granted. The review finds the CMC editorial changes in the proposed label acceptable. The supplement is recommended for approval from a CMC standpoint.

4. Nonclinical Pharmacology/Toxicology

There were no changes proposed in the Nonclinical Toxicology section of the labeling (section 13). There is no Nonclinical Pharmacology/Toxicology review for this supplement.

5. Clinical Pharmacology/Biopharmaceutics

The Office of Clinical Pharmacology Pharmacometrics Review (J. A. Grillo, 8/1/2014) examined results from the efficacy study (ELT112523) and commented: "Pharmacokinetic sampling was not collected in this trial. In addition, the applicant did not submit any other clinical pharmacology related information or analyses in this application. The applicant did propose several grammatical changes to section 12.3 (Pharmacokinetics) of the approved labeling (i.e., changed (b) (4) to "compared with" throughout the section (6 instances) and replaced (b) (4) with parentheses in one instance). These proposed labeling changes were evaluated from a clinical pharmacology perspective and are acceptable. We agree with the proposed dose modifications for ethnicity and hepatic impairment because they are consistent with current recommendations under the ITP indication that were based on dedicated pharmacokinetic (PK) trials in these populations."

The review concluded that there is sufficient clinical pharmacology and biopharmaceutics information provided in this efficacy supplement to support a recommendation of approval of PROMACTA for the proposed new indication.

6. Clinical Microbiology

No clinical microbiology information was submitted for this application.

7. Clinical/Statistical- Efficacy

The detailed Clinical Review of this supplemental application was conducted by A. Dmytrijuk, M.D. (Clinical Review, final signature 8/18/2014). Medical Team Leader Secondary Review of the application was completed by K. Robie Suh (signed 8/22/2014). Statistical Review was conducted by X. Jiang (final signature 8/1/2014). The primary evidence for efficacy is from Study ELT112523, a single-arm, open-label, single-center, non-randomized, study of eltrombopag in patients with severe aplastic anemia (SAA) and thrombocytopenia refractory to prior immunosuppressive therapy.

As described in Dr. Dmytrijuk's review, ELT112523 was the primary study used to support the safety and efficacy of eltrombopag for the treatment of patients with SAA who had an insufficient response to IST. ELT112523 was a single arm, single center, open label study which enrolled 43 patients with SAA who had an insufficient response to at least one prior IST and who had a platelet count ≤30,000/μL. Eltrombopag was administered at an initial dose of 50 mg once daily for 2 weeks and was increased every 2 weeks up to a maximum dose of 150 mg once daily. The dose of eltrombopag was adjusted based on platelet counts with the goal to maintain the platelet count in the ≥ 50,000/μL-<200,000/μL range. Eltrombopag was discontinued after 16 weeks of therapy if no hematologic response was observed. The primary endpoint of study ELT112523 was hematologic response assessed after 12 weeks of treatment with eltrombopag. Hematologic response was defined as meeting one or more of the following criteria:

- Platelet count increases to >20,000/μL above baseline, or stable platelet counts with transfusion independence for a minimum of 8 consecutive weeks.
- Hemoglobin increase by ≥1.5g/dL, or a reduction in ≥4 units of red blood cell (RBC) transfusions for 8 consecutive weeks.
- ANC increase of 100% (pre-treatment levels < 500/μL) or an ANC increase > 500/μL at least once.

Mean age of patients in the study was 45.5 years, 56% were males, median time since diagnosis was about 31 months, about 90% had platelets and/or RBC transfused at referral, and 84% had had ≥2 prior immunosuppressive therapies before entering the study.

The primary efficacy analysis is shown below:

Table 13 Primary Endpoint: Investigator-Assessed Response

	Eltrombopag (N=43)
Response, n (%)	17 (40)
95% CI [a]	(25,56)

Data Source: Table 2.0010

a. Confidence Intervals for percentage using Klopper-Pearson method

Sponsor's table, report for Study ELT112523

As Dr. Dmytrijuk describes in the Clinical Review:

A total of 17/43 patients (40%) met the hematologic response criteria in at least one lineage at the 12-16 week assessment time point. There was one patient (Patient (b) (6)) who had a tri-lineage hematologic response and 3 patients (Patients (b) (6)) who had bi-lineage responses of the platelets and neutrophils. No other combination of bi-lineage responses in the blood cell lines was observed in this study. There were 13 patients who had a response in one blood cell lineage. The median time to initial response was 12 weeks (range, 8-14 weeks).

Analyses of secondary endpoints, including reduction in transfusions, were consistent with a benefit of eltrombopag. The Medical Team Leader Secondary Review (K. Robie Suh, 8/22/2014) indicates that, based on the 120-Day Safety Update information, among 14 patient responders who continued eltrombopag into the extension portion of the study, 5 patients were tapered off eltrombopag due to trilineage response and 4 patients continue on eltrombopag.

Regarding efficacy Dr. Dmytrijuk commented in the Clinical Review:

The efficacy of eltrombopag therapy for the treatment of patients with SAA who had an insufficient response to previous IST was demonstrated in trial ELT112523. Nearly all patients (36/43, 83%) had at least 2 prior therapies for their SAA. In the trial ELT112523, there were 17/43 (40%) of patients with SAA who had an insufficient response to prior IST who had a hematologic response after a median 12 weeks (range 8-14 weeks) of therapy with eltrombopag. There were 4/17 responders who had multi-lineage responses. As might be expected, among those patients who responded there were 8 patients who had a platelet response based on stable platelet counts with transfusion independence for a minimum of 8 consecutive weeks. Three patients had a response in platelet counts, i.e., they had a platelet count increase > 20,000/μL above baseline. However, there were 8 patients who had a neutrophil response. There were 3 patients who had a response based on a reduction in ≥ 4 units of RBC transfusions for 8 consecutive weeks. Clinically a reduction in transfusion requirements is important due to the decreased use of these medical resources. An increase in neutrophil count can help prevent infections in these patients. The starting dose of eltrombopag was 50mg orally once daily. The starting dose of eltrombopag was decreased for patients of East Asian ancestry, i.e., 25mg orally once daily, similar to the labeled recommendation for the dosing of eltrombopag in the approved eltrombopag indications, i.e., immune thrombocytopenic purpura (ITP) and chronic hepatitis C virus infection (HCV). In trial ELT112523, 40 patients were dose escalated to the maximum protocol allowed dose of eltrombopag 150mg orally once daily. There were 3 patients who reached a maximum eltrombopag dose of 125mg orally once daily. Although it is difficult to do cross study comparisons, the efficacy results of trial ELT112523 are generally similar to those from published literature. These results demonstrate that eltrombopag can be effective treatment for patients with SAA who have had an insufficient response to therapy.

The Statistical Review (X. Jiang, 8/1/2014) cited the limitations of this single arm study but found no major statistical issue that impacted the overall conclusions. The Statistical Review deferred the evaluation of safety and benefit/risk to the clinical review team. The Statistical Review Conclusions and Recommendations states:

5.3 Conclusions and Recommendations

No statistical comparison was conducted in Study ELT112523 and therefore no statistical inference can be drawn from the study. The nature of single-center Study ELT112523 may not be able to provide a better basis for the subsequent generalization of its findings. However, given the rare disease nature of SAA, whether the adequacy of Study ELT112523 and the results from the study provide a favorable benefit to risk ratio to support an approval of Eltrombopag for the proposed indication will be determined by the clinical review team.

8. Safety

The detailed review of the safety data in the supplemental application was conducted by A. Dmytrijuk, M.D. (Clinical Review, final signature 8/18/2014). Medical Team Leader Secondary Review of the application was completed by K. Robie Suh (signed 8/22/2014).

The major safety findings from Dr. Dmytrijuk's review are summarized below:

Reviewer comment for section 7: In ELT112523 the most common adverse events (AEs) occurring in ≥20% of patients were nausea, fatigue, cough, diarrhea and headache. The most common serious adverse events (SAEs) occurring in ≥ 5% patients were febrile neutropenia, sepsis and viral infection. There were 6 deaths reported during the study. There were no subjects who died while receiving eltrombopag therapy. There were 2 patients who died within 30 days of the last dose of eltrombopag (both deaths related to sepsis) and 4 patients died > 100 days after the last dose of eltrombopag (2 deaths due to sepsis, 1 AML (patient (b) (6)) and 1 cause of death was unknown but occurred 116 days from the last dose of eltrombopag). There were 7/43 patients who had new cytogenetic abnormalities reported, including 5 patients who had complex changes in chromosome 7. Patient (b) (6) was on eltrombopag therapy for a period of 3 months and was noted to have abnormal hematopoietic maturation at baseline. There were 3 patients with baseline cytogenetic abnormalities. There were no thromboembolic AEs reported. Hepatobiliary AEs grade 3 or 4 elevations in serum liver transaminases or elevated serum bilirubin levels were reported in 6/43 patients according to NCI-CTCAE v.3.0 Criteria. In two patients (Patients (b) (6)) had alanine aminotransferase (ALT) elevation > 3 x upper limit of normal (ULN) and total bilirubin > 1.5 x ULN (see section 7.3.4 for a detailed discussion of these 2 cases). However, in both cases the indirect bilirubin was elevated. There were 4 patients in which AEs lead to premature discontinuation of eltrombopag therapy (including cataract, abdominal discomfort, hepatitis B infection and sepsis). There were no thromboembolic adverse reactions reported. There were 2 patients age <18 years enrolled in the study. Both patients were non-responders. In general, therapy with eltrombopag in patients with SAA resulted in similar frequencies and types of adverse reactions.

Findings of the MTL Secondary review (K. Robie Suh, 8/22/2014) were generally consistent with those of Dr. Dmytrijuk's primary Clinical Review.

9. Advisory Committee Meeting

There was no Advisory Committee meeting held for this supplemental application.

10. Pediatrics

Eltrombopag has been granted Orphan Drug Designation for treatment of aplastic anemia and therefore, the sponsor is exempt from requirement for pediatric studies of Promacta under Pediatric Research Equity Act (PREA). The sponsor does have two ongoing trials in patients with severe aplastic anemia in which enrollment of patients age ≥2 years is allowed. As stated in the Medical Team Leader Secondary Review (K.Robie Suh, signed 08/22/2014) the sponsor should be encouraged to complete those studies and submit the study reports.

The sponsor currently is investigating eltrombopag for use in pediatric patients with chronic idiopathic thrombocytopenic purpura (ITP) under a Written Request for Pediatric Studies (originally issued 1/25/2010; amended 11/29/2011).

11. Other Relevant Regulatory Issues

The Division of Good Clinical Practice Compliance (DGCPC), Office of Scientific Investigations (OSI) (A. Orencia, M.D., final signature 7/21/2014) conducted an inspection of the one clinical site for Study ELT112523 with audit of records for 25 subjects. The inspection found that in general the site appeared to be in compliance with Good Clinical Practices, gave a preliminary regulatory classification No Action Indicated (NAI) and recommended that, "The study data collected from this clinical site appears reliable in support of the requested indication."

12. Labeling

In the Clinical Review (A. Dmytrijuk, final signature 0818/2014) gives the following key recommendations for the labeling:

The key proposed labeling changes include:

- The proposed indication should state that eltrombopag is indicated for the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy. This wording should be used in the Highlights section, Indications and Usage section § 1.3 subheading and in other sections of the label which refer to this indication.
- In section 2 Dosage and Administration § 2.3 the dosing of eltrombopag should be clarified for patients who achieve tri-lineage response including transfusion independence lasting at least 8 weeks. For these patients the dose of eltrombopag should be reduced by 50%.
- In section 6.1 Clinical Trial Experience the word "complex" should be added to describe the cytogenetic changes that were observed in 5 patients who had changes in chromosome 7.
- In section 14 Clinical Studies § 14.3 the wording regarding bi-lineage or tri-lineage responses should be clarified to state that these responses were observed in 4/43 (9%) of patients.

The package insert and Medication Guide changes were discussed and final wording developed at labeling meetings and discussions involving the entire review team.

13. Recommendations/Risk Benefit Assessment

The sponsor is seeking approval of eltrombopag for the treatment of cytopenias in patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy. To support the proposed indication the sponsor has submitted results of an open-label, single-center, non-randomized, study (ELT112523) of eltrombopag in patients with severe aplastic anemia (SAA) and thrombocytopenia who have had an insufficient response to immunosuppressive therapy. As stated in the Clinical Review of this application (A. Dmytrijuk, final signature 08/18/2014):

> The benefit/risk assessment for eltrombopag for the proposed indication favors the approval of eltrombopag. Although study ELT112523 was a small study this could be expected due to the rarity of the disease being studied. All patients were enrolled and treated at a single center, i.e., the National Institutes of Health which has internationally recognized expertise in the treatment of patients with SAA. The study was initiated on June 23, 2009 and the data cutoff date was June 1, 2013. In study ELT112523 in patients with SAA who had insufficient responses to prior IST there were 17/43 (40%) patients who responded to eltrombopag therapy and 4/43 patients who had multi-lineage hematologic responses. Overall, therapy with eltrombopag resulted in adverse events that were similar to those in the current eltrombopag product label in terms of grade and frequency.

There was no clear evidence that eltrombopag had a causative effect on cytogenetic abnormalities reported during the study. In SAA there is generally a high rate of background rate of cytogenetic abnormalities in patients with SAA. In aplastic anemia 4-15% of patients have baseline abnormal cytogenetics. (Gupta 2006) In one study 69 patients with acquired severe aplastic anemia underwent cytogenetic examination of bone marrow cells at the time of diagnosis and after IST. IST consisted of anti-lymphocyte globulin (ALG) with or without corticosteroids in 40 patients, 8 were treated only with corticosteroids and 21 were treated with the combination of ALG plus cyclosporine plus corticosteroids. In this study 51/69 (74%) of patients with normal cytogenetics at baseline had normal cytogenetics after IST. There were 7/69 (10%) of patients who had a normal baseline cytogenetic evaluation and subsequently at least one abnormal cytogenetic analysis after IST. There were 3/69 (4%) of patients who had a baseline abnormal cytogenetic evaluation which remained abnormal after IST. There were 8/69 (12%) of patients with an abnormal baseline in which the cytogenetics reversed to normal after IST. The most frequent abnormality was trisomy 8 (n = 8) followed by monosomy 7 (n = 2). In this study 3 patients developed acute leukemia of which 2 patients had baseline normal cytogenetic and subsequent abnormal cytogenetics after IST and 1 patient had baseline abnormal cytogenetics which remained abnormal after IST. (Mikhailova 1996) Similarly, in ELT112523 there were 6/43 (14%) of patients who had a baseline normal cytogenetic evaluation followed by an abnormal cytogenetic evaluation after eltrombopag therapy. The baseline cytogenetic sample was not adequate for evaluation in one patient. There were 5 patients who had complex changes in chromosome 7. One patient died due to myelodysplastic syndrome/acute myeloid leukemia. Two other patients received bone marrow transplants. Deaths that were reported in study ELT1123 were primarily due to sepsis which can be expected in this generally neutropenic patient population.

Although study ELT112523 is a small (n = 43), single arm study it provides convincing evidence that eltrombopag therapy can increase blood counts (platelets, hemoglobin or white blood cells) in patients with IST-refractory SAA. The small number of patients enrolled in the study can be expected due to the rarity of the disease. In addition, current treatment options including hematopoietic stem cell transplant for patients with SAA, with the exception of supportive care options, are immunosuppressive which increase the risk for infections. Thus, there is an unmet need for other therapies which do not increase the risk of infection and are well tolerated. In contrast to IST therapies, eltrombopag appears to stimulate hematopoiesis, which offers a mechanistically new treatment option for patients with SAA who are refractory to IST. Also, about a quarter of patients with severe aplastic anemia remain pancytopenic despite immunosuppressive therapy. (Desmond, 2014) As noted in ELT112513 40% of patients responded to eltrombopag therapy and approximately 10% of patients in this study had a tri-lineage response.

The recommended dose is 50 mg once daily (25 mg in patients of East Asian ancestry or with hepatic impairment) and dose is adjusted to maintain platelet count $\geq$50 x 10^9/L but not to exceed 150 mg daily.

Final wording of the labeling should consider the input of the reviews discussed above and be negotiated with the sponsor.

Though no post-marketing requirements are recommended, Dr. Dmytrijuk's clinical review recommends that ongoing study ELT116643 should be completed and submitted for review. The review states:

I recommend that the sponsor complete and submit for review the ongoing study ELT116643 titled, "Eltrombopag Added to Standard Immunosuppression in Treatment Naïve Severe Aplastic Anemia" as a Post-Marketing Commitment (PMC). Briefly, this study is a phase1/2, open-label, single arm, single-center study of eltrombopag administered in combination with ATG and cyclosporine. In this study the sponsor plans to enroll up to 62 patients with SAA who are age ≥ 2 years. Patients are to receive eltrombopag orally once daily, starting at 150mg in patients age 12-85 years, 75mg for patients age 6-11 years and 2.5mg/kg for patients age 2-5 years on day 14 after the start of IST to avoid overlap with the known transient hepatotoxicities associated with IST. The starting dose of eltrombopag will be reduced by 50% in patients of East-Asian ancestry. The planned duration of therapy with eltrombopag is 6 months. The dosing of eltrombopag will be adjusted for toxicities according to the approved eltrombopag label and to maintain platelet counts < 200,000/μL. The primary efficacy endpoint is the rate of complete hematologic response at six months of therapy. Serial blood counts will be obtained. A complete response will be defined as meeting the following criteria, i.e., ANC > 500/μL, Hgb level increase by > 1.5g/dL and platelet count > 20,000/μL based on 2 serial blood counts at least one week apart. Peripheral blood smears will be evaluated for histologic abnormalities and bone marrow biopsies will be performed at landmark time points of 3 months and 6 months after therapy. The primary efficacy endpoint and AEs will be described descriptively. This study was initiated June 14, 2012 and has an expected completion date of May 2015.

As noted in my Medical Team Leader Secondary Review (K. Robie Suh, signed 8/22/2014) the sponsor also has a more recently initiated ongoing study ELT116826 in patients with refractory severe aplastic anemia and the sponsor should also be encouraged to complete and submit this study for review.

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/s/

KATHY M ROBIE SUH
08/23/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22291Orig1s012

CLINICAL REVIEW(S)

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: August 18, 2014

From: Kathy M. Robie Suh, M.D., Ph.D.
Medical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products

Subject: Medical Team Leader Secondary Review
NDA 22-291/ S-012 (letter date 2/27/2014; received 2/27/2014) – Efficacy Supplement
Promacta (eltrombopag olamine)
Proposed indication: treatment of cytopenias in patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy

To: NDA 22-291

Background:
Eltrombopag (Promacta) is an orally available small molecule thrombopoietin receptor (TPO-R) agonist approved 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 (accelerated approval, 11/20/2008; converted to full approval 2/25/2011), The approved dose is 50 mg once daily (25 mg in patients of East Asian ancestry or with hepatic impairment) and dose is adjusted to maintain platelet count $\geq$50 x 10^9/L but is not to exceed 75 mg daily.
- the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. The approved dose is 25 mg once daily for all patients and dose is adjusted to achieve platelet count required to initiate antiviral therapy, not to exceed 100mg daily. (11/16/2012).

Severe aplastic anemia (SAA) is a life-threatening, acquired bone marrow failure disease characterized by tri-lineage marrow hypoplasia and a lack of hematopoietic stem and progenitor cells (HSPC) due to an immune-mediated attack on the bone marrow.
The disease is often fatal, due to infection or hemorrhage. Currently used treatments include intensive immunosuppressive therapy (IST) with horse anti-thymocyte globulin

and cyclosporine (ATG/CsA), or hematopoietic stem cell transplantation (HSCT), where appropriate and possible. However, about half of patients will either not have an initial response or will relapse. In the current submission the sponsor seeks approval of eltrombopag for treatment of cytopenias in patients with severe aplastic anemia (SAA) who have had an insufficient response to immunosuppressive therapy. The sponsor was granted Breakthrough Therapy designation for eltrombopag for patients with SAA based on an unmet medical need for therapy for these patients and on published data from an investigator-initiated, single-arm, phase II study in 25 patients with SAA refractory to immunosuppressive therapy. (See review by Dr. A. Dmytrijuk, IND 63293, 1/16/2014) (letter issued 1/27/2014). The sponsor requests Priority Review of this application and the Division has determined that priority review should be granted. Also, eltrombopag has been granted Orphan Product Designation (November 8, 2013) for treatment of aplastic anemia.

To support the proposed indication the sponsor has submitted results of an open-label, single-center, non-randomized, study of eltrombopag in patients with severe aplastic anemia (SAA) and thrombocytopenia (NIH 09-H-0154/ELT112523). Additional data are provided from an ongoing study (NIH 12-H-0150/ELT116643) in patients with SAA who are receiving standard treatment with hATG/cyclosporine in combination with eltrombopag and a completed placebo-controlled Phase I/II study (PMA112509) in patients with advanced myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).

The primary Clinical Review of this application has been conducted by Dr. A. Dmytrijuk (review signed in DARRTS 8/18/2014). Please see Dr. Dmytrijuk's review for detailed presentation and discussion of the efficacy and safety results for this supplemental application. The major findings of the studies and issues for the application are summarized below.

Summary of Review Findings of Study NIH 09-H-0154/ELT112523 (Study ELT112523)

Study NIH 09-H-0154/ELT112523, titled "A Pilot Study of a Thrombopoietin-receptor Agonist (TPO-R agonist), Eltrombopag, in Aplastic Anemia Patients with Immunosuppressive-therapy Refractory Thrombocytopenia," was an open-label, single center (NIH Clinical Center), non-randomized, Phase II, dose modification study of eltrombopag in adult patients with SAA with insufficient response to prior immunosuppressive therapy. The study was conducted from June 23, 2009 to June 1, 2013. The study enrolled patients age $\geq$18 years (amended 9/27/2012 to allow $\geq$12 yrs) who had SAA and thrombocytopenia with a platelet count $\leq$30,000/uL after having received at least one treatment course of horse or rabbit ATG/cyclosporine. Important exclusion criteria were: having a PNH clone size in neutrophils of $\geq$50%, Fanconi anemia, serum creatinine >2.5 mg/dL, bilirubin >2.0, SGOT or SGPT >2 times upper limit of normal (ULN) (changed to 5 times ULN in November 2009 amendment), recent malignancy, poor performance status, HIV positivity, pregnant or nursing, significant

cardiovascular disease history (congestive heart failure, myocardial infarction, chronic arrhythmia requiring therapy), history of thrombosis, and treatment with horse or rabbit ATG or Campath with 6 months prior to study entry. Concurrent stable treatment with cyclosporine or G-CSF was permitted. The initial protocol planned enrollment of up to 20 patients; however, this was amended in April 2012 to include up to 25 additional patients. Treatment was initiated with an eltrombopag dose of 50 mg orally once daily on an empty stomach (25 mg daily in patients of East Asian ancestry). If platelet count did not increase by 20,000/uL or no decrease in platelet transfusion requirements after 2 weeks of therapy, dose was to be increased by 25 mg every 2 weeks to a maximum of 150 mg daily for non-East Asian patients or 75 mg daily for East Asian patients. Dose interruption was allowed for certain situations such as infection requiring antibiotics and liver function abnormalities. Patients were to be permanently discontinued if occurrence of any of: DVT or PE, stroke, myocardial infarction, or persistent SGOT/SGPT elevation >6 times ULN. The primary efficacy endpoint was investigator-assessed treatment response rate at the primary response assessment, which was to be at the end of 12 weeks of treatment. In the initial protocol treatment response was defined as platelet count increases to 20,000/uL above baseline at three months, or stable platelet counts with transfusion independence for a minimum of 8 weeks. On January 20, 2011 the treatment response definition was expanded to also include a response based on RBC and a response based on neutrophil counts. The final primary endpoint was stated as follows:

> The primary endpoint was Investigator-assessed response rate at the Primary Response Assessment defined as follows:
>
> - Platelet response - platelet count increases to 20 Gi/L above baseline, or stable platelet counts with transfusion independence for a minimum of 8 weeks; or
> - Erythroid response - an increase in hemoglobin by ≥1.5 g/dL in subjects with a pre-treatment hemoglobin <9 g/dL, or an absolute reduction of at least 4 RBC transfusions for 8 consecutive weeks, compared to the number of transfusions in the 8 weeks pretreatment; or
> - Neutrophil response - ≥100% increase in ANC in subjects with a pre-treatment ANC of < 0.5 Gi/L, or an ANC increase >0.5 Gi/L.

The protocol was amended several times while the trial was underway. The final protocol amendment was made on February 5, 2013. Details of all the successive amendments were not provided; however, most changes appeared to be administrative (e.g., change in Associate Investigators), updates of the Investigator Brochure, or clarifications. Notable changes during the study included: change in the exclusion criterion for liver function tests mentioned above, enrollment age change to ≥12 years, change in the primary efficacy endpoint definition and analysis as described above, addition of a provision to allow patients who achieve a favorable response to therapy to continue eltrombopag after completion of study participation, increase in target enrollment from maximum of 30 to

maximum of 45 patients. The primary efficacy analysis plan for evaluating efficacy on 25 patients was not changed in the Statistical Analysis Plan and for the study report the first 25 patients enrolled and treated were referred to as Cohort 1 and the additional enrolled and treated patients were referred to as Cohort 2. Most of the presentation of results in the study report is for the total 43 treated patients.

Study NIH 09-H-0154/ELT112523 was conducted from June 23, 2009 to June 1, 2013. A total of 44 patients were enrolled and 43 were treated. The disposition of patients enrolled in the study is summarized in the following table:

Table 5 Summary of Subject Status and Reason for Study Withdrawal

	Eltrombopag (N=43)
Subject Status, n (%)	
Ongoing in Study	12 (28)
Completed	6 (14)
Died	6 (14)
Withdrawn from Study	19 (44)
Primary reason for study withdrawal [a], n (%)	
Subject reached protocol defined study withdrawal criteria[b]	14 (33)
Adverse event	2 (5)
Lost to follow-up	1 (2)
Withdrew consent	1 (2)
Lack of efficacy	1 (2)

Data Source: Table 1.0020

a. Subjects can have only one primary reason for withdrawal.
b. Referred to other therapies or transplant, had a cytogenetic abnormality detected or had evidence of dysplasia.

Sponsor's table, report for Study ELT112523

Among the 43 patients treated, 19 discontinued study prematurely, 14 due to meeting pre-defined withdrawal criteria, 2 due to adverse events (abdominal discomfort; liver function test abnormal/Hepatitis B), one lost-to followup, one withdrew consent and one due to lack of efficacy. Among the 14 who met pre-defined withdrawal criteria all completed the 12 weeks treatment specified for primary efficacy evaluation but did not complete all of the followup evaluations. Among these 14 patients 2 were responders and 12 were non-responders.

Demographic and baseline characteristics of the treated patients are summarized in the following table:

Demographic and Baseline Characteristics of Patients in Study NIH 09-H-0154/ELT112523

	Eltrombopag 50 mg N=43

Age, yrs	
Mean	45.5
Median	45.0
Minimum – maximum	17-77
Age group (yrs), n (%)	
<18	2 (5)
18-64	27 (63)
65-74	12 (28)
≥75	2 (5)
Sex, n (%)	
Female	19 (44)
Male	24 (56)
Race/Ethnicity	
White	20 (47)
Black	13 (30)
Hispanic	9 (21)
Asian	1 (2)
Disease characteristics at screening:	
Time since diagnosis, median (range), mos	30.9 (10-190)
Platelets transfused at referral, n (%)	39 (91)[a]
RBC transfused at referral, n (%)	37 (86)[b]
Platelets and RBC transfused at referral, n (%)	35 (81)[c]
Karyotype, n (%)	
Normal	38 (88)
Abnormal	3 (7)
Insufficient metaphases	1 (2)
Baseline hematology laboratory values, median (range)	
Platelets ($x10^9$/L)	20 (6-90)
Neutrophils ($x10^9$/L)	.58 (0.07-2.81)
Hemoglobin (g/dL)	8.4 (6.6-13.8)
Reticulocytes($x10^9$/L)	24.3 (1.7-96.9)
Patients with severe cytopenias, n (%)	
Neutropenia <$0.5x10^9$/L	18 (42)
Thrombocytopenia <$20x10^9$/L	18 (42)
Anemia <10.0 g/dL	35 (81)
Number of prior immunosuppressive therapies, n (%)	
≥1	43 (100)
≥2	36 (84)
≥3	14 (33)
≥4	3 (7)

Reviewer's table based on sponsor's tables in report for Study ELT112523

Mean age was about 45.5 years. There were a few more males than females. Only 2 patients were less than 18 years of age (both 17 yrs). The great majority of patients were receiving platelet and RBC transfusion at referral (median of 4 platelet transfusions/month and 4 RBC transfusions/8 weeks) and most patients (84%) had received at least 2 prior immunosuppressive therapies (IST). The most common prior IST were: horse antithymocyte globulin (ATG) based regimen (41 patients), rabbit ATG based regimen (25 patients), alemtuzumab 15 patients), cyclophosphamide (6 patients), and non-specified ATG (1 patient). Ninety-three percent (93%) of patients had also used other medications for SAA including androgens (e.g., danazol), 16 patients, steroids,, daclituzumab, mycophenolate, tacrolimus, sirolimus and immunoglobulin (IVIG and WINRHO), supportive care agents (GM-CSF, Neupogen, Nplate, Procrit), and methotrexate.

Most patients (91%) had one or more past medical conditions, most commonly: nausea (8 patients), epistaxis (6 patients), neutropenic fever (6 patients), easy bruising (5 patients), hypertension (5 patients), and insomnia, fatigue, headaches, diarrhea and anxiety (4 patients each). Three patients had past history of iron overload. Forty (93%) of the patients had one or more current medical conditions, most commonly: iron overload (20 patients), fatigue (17 patients), hypertension (9 patients), depression (7 patients), anxiety (6 patients), and epistaxis (6 patients). The most common concomitant medications were: paracetamol (33 patients), deferasirox (20 patients), valcyclovir (14 patients), diphenhydramine (13 patients), Benadryl (12 patients) and ciprofloxacin (10 patients). Seven patients were receiving deferoxamine.

Efficacy results:
The sponsor's primary efficacy analysis for the study is shown in the table below:

Table 13 Primary Endpoint: Investigator-Assessed Response

	Eltrombopag (N=43)
Response, n (%)	**17 (40)**
95% CI [a]	(25,56)

Data Source: Table 2.0010
a. Confidence Intervals for percentage using Klopper-Pearson method

Sponsor's table, report for Study ELT112523

Among the 17 patients recorded as responders, 13 achieved response at Week 12 and 4 at Week 16. Criteria for response achieved by these patients are summarized in the following table:

Summary of Response at Week 12-16 Visit

Response due to:	Number of Patients (%)
Platelets only	7 (41)
RBC only	2 (12)
Neutrophils only	4 (24)
Platelets/RBC	0
Platelets/Neutrophils	3 (18)
Neutrophils/RBC	0
Platelets/RBC/Neutrophils	1 (6)

Reviewer's table based on data in sponsor's report for Study ELT112523

Most responders (14 patients) achieved response based on platelets, neutrophils or platelets+neutrophils. Only 3 patients achieved an RBC response (2 RBC alone and 1

RBC along with platelets and neutrophils), all based on decrease in RBC transfusion requirement. For the 11 patients who achieved a platelet response [platelet count increases to 20,000/uL above baseline at three months, or stable platelet counts with transfusion independence for a minimum of 8 weeks], 8 achieved response by avoiding platelet transfusion and 3 by increased platelet count. Among the 18 patients who started the study with severe neutropenia (ANC <0.5x 10^9/L) 8 achieved neutrophil response based on at least a 100% increase or an absolute increase > 0.5 x 10^9/L in ANC. One patient showed a tri-lineage response (platelets/RBC/neutrophils) at primary efficacy assessment. At best assessment, 4 patients (b) (6) showed a tri-lineage response and 4 showed a bi-lineage response. For 14 of the 17 responders, including all 8 bi-lineage and tri-lineage responders, the last response assessed was the same as the best response. The response did not last in 3 of the uni-lineage responders (b) (6) (b) (6) (relapse at Month 3 extension visit). Among the 17 responders, the 14 who maintained their response to the end of the study continued eltrombopag in the extension part of the study.

Almost all of the patients required platelet transfusion (40/43) and/or RBC transfusion (38/43) at some time during the study. Among the 17 responders, mean maximum duration of platelet transfusion independence during treatment (including the extension phase) was 363 days (median, 200 days; range 8-1096 days); among the 26 non-responders, mean maximum duration of platelet transfusion independence was 30 days (median, 22.5 days; range 7-84 days). For RBC transfusions, among the 17 responders, mean maximum duration of transfusion independence during treatment (including the extension phase) was 340 days (median, 208 days; range 15-1082 days); among the 26 non-responders, mean maximum duration of transfusion independence was 38 days (median, 29 days; range 8-115 days).

It should be noted that no patients who started the study transfusion independent (platelet or RBC) became transfusion dependent during the study. Four patients in the study (2 responders and 2 non-responders) were platelet transfusion independent at baseline and they remained so during the study. Six patients in the study (4 responders and 2 non-responders) were RBC transfusion independent at baseline and they remained so during the study.

At time of the study report, 4 responders who achieved a tri-lineage response had tapered off eltrombopag. With a median follow-up of 8.1 months (range, 7.2-10.6 months) since discontinuation of eltrombopag, all remained in response. An additional responder (subject (b) (6) with platelet/ANC response discontinued eltrombopag due to a possible cataract continued to have improvement in platelet and ANC counts and also showed improvement in hemoglobin 6 months later. Finally, one responder (subject (b) (6)) stopped eltrombopag treatment after about 22 months and continued to have response 33 days later reported in the 120-Day Safety Update.

Transfusion information for the four patients who were tapered off eltrombopag due to having met 'tri-lineage hematopoiesis criteria' (platelets >50x10^9/L, hemoglobin >10g/dL and ANC >1.0x10^9/L) for at least 8 weeks is summarized in the following table based on the initial sNDA submission. In the 120-Day Safety Update, one additional patient is said to have tapered off eltrombopag due to tri-lineage response and maintained a response.

Summary of Platelet and RBC Transfusion Course for Four Patients who were Tapered Off Eltrombopag Due to Meeting Criteria for Tri-lineage Hematopoiesis

Subject	Platelet transfusions		RBC Transfusions		Months off eltrombopag
	Baseline	During study	Baseline	During study	
(b) (6)	3 in the 35 days prior to study entry	None for 43.4 mos	1 in the 35 days prior to study entry	None for 42.9 mos	7.4 mos
	4 in the 35 days prior to study entry	None for 40.6 mos	None in the 35 days prior to study entry	None for 41.8 mos	7.2 mos
	1 in the 35 days prior to study entry	None for 37.4 mos	1 in the 35 days prior to study entry	None for 34.8 mos	10.6 mos
	2 in the 35 days prior to study entry	None for 30.1 mos	1 in the 35 days prior to study entry	None for 30.1 mos	8.8 mos

Reviewer's table based on data in sponsor's report for Study ELT112523

There did not appear to be marked differences in disease characteristics between the responders and non-responders. Percentage of patients requiring transfusion at referral was slightly less among the responders (76% for RBC; 76% for platelets and RBC) than among non-responders (92% for RBC; 85% for platelets and RBC).

Examination of efficacy for patients enrolled prior to the amendment increasing sample size (n=25; Cohort 1) and those enrolled afterwards (N=18; Cohort 2) showed a response rate of 44% (11/25) for Cohort 1 and 33% (6/18) for Cohort 2. Demographic features of the two cohorts were similar except for a slightly older age in Cohort 1 (46.7 yrs) as compared to Cohort 2 (43.9 yrs) and more females in Cohort 1 (48%) as compared to Cohort 2 (39%). Percentage of patients receiving transfusion at baseline referral was slightly greater in Cohort 2 (94% for RBC; 89% for platelets and RBC) as compared to Cohort 1 (80% for RBC; 76% for platelets and RBC). Neutropenia at baseline was a bit more common in Cohort 2 (50%) than in Cohort 1 (36%). Number and type of prior IST medications were similar in the two cohorts, except for slightly greater use in Cohort 1 of rabbit ATG based therapy (68.0%) and alemtuzumab (40.0%) and less use of

cyclophosphamide (8.0%) as compared to in Cohort 2 (rabbit ATG, 44.4%; alemtuzumab, 27.8%; cyclophosphamide, 22.2%).

Results of bone marrow examination for responder patients showed hypocellular marrow at baseline for 15 of 17 patients (tri-lineage hypoplasia or nearly absent hematopoiesis in 9). Repeat examinations during the study (at primary assessment and every 6 months thereafter) showed improvement in some and no apparent worsening in any. Four responders noted to have "dysplasia, dyspoiesis or dyspoietic changes" at baseline had no new cytogenetic changes detected during the study or were diagnosed as having myelodysplasia. One responder (subject (b) (6)) had dysplasia noted and a deletion 13 cytogenetic changed detected at day 419 bone marrow examination. This patient subsequently received a bone marrow transplant.

Although pediatric patients ≥12 years of age were permitted to participate in the study, only two pediatric patients were enrolled. These were patients (b) (6) a 17 year old Black male, and patient (b) (6) a 17 year old Hispanic male. Maximum dose was 150 mg for both, but neither patient had a response at Day 84 evaluation. Patient (b) (6) experienced multiple adverse reactions, including serious reactions of febrile neutropenia and bilateral pneumonia and multiple non-serious events. Patient (b) (6) experienced non-serious events of pruritus, nausea, insomnia and ganglion cyst.

For most of the study compliance was not formally tracked. Beginning in November 2012 study staff started recording pill counts dispensed and returned at each visit.

Safety results:
In Study ELT112523 a total of 43 patients received eltrombopag. Among these, 40 (93%) were escalated to the maximum daily dose of 150 mg and 3 patients received a maximum dose of 125 mg. The median time on treatment (including for non-responders) was 3.6 months (mean, 7.5 months, range 2-37 months). Ten patients were treated for <3 months, 33 for 3-6 months, 11 for 6-12 months and 7 for >12 months.

In the study 40 (93%) patients experienced at least one adverse event (AE) while on therapy. The most common AEs were nausea (14 patients), fatigue (12 patients), cough (10 patients), diarrhea (9 patients), and headache (9 patients). In 4 patients adverse event led to treatment discontinuation (1 sepsis; 1 possible cataract; 1 abdominal discomfort; 1 acute hepatitis B) and in 3 others led to dose interruption (1 nausea and vomiting; 1 elevated liver function tests, febrile neutropenia, lower abdominal pain; 1 neutropenia, hypotension, infection, clostridium difficile colitis). Two patients had 2 interruptions and 1 had 1 interruption; duration of interruption ranged from 1 to 10 days. A total of 14 (33%) patients experienced serious adverse events (SAE). These included 6 cases of febrile neutropenia, 2 cases of sepsis (1 fatal), 2 cases of viral infection, and one case each of abdominal discomfort, lower abdominal pain, anemia, aplastic anemia (fatal), biliary colic, Clostridium difficile colitis, pneumonia, septic shock (fatal), and staphylococcal sepsis. Only one SAE (abdominal discomfort) was considered treatment-

related by the investigator. Among all AEs, the most common events considered treatment-related were nausea, headache and diarrhea. There were a total of 4 deaths during the study as shown in the sponsor's following table:

Table 26 Summary of Deaths

		Eltrombopag (N=43)	
Subject ID	**Time of Death**	**Time from last dose (Days)**	**Primary Cause of Death**
On-Therapy			
(b) (6)	≤30 days post-treatment	22	Disease under Study; sepsis/infection
	≤30 days post-treatment	8	Disease under Study; sepsis/infection
Post-Therapy			
(b) (6)	>30 days post-treatment	195	MDS/AML
	>30 days post-treatment	112	Disease under Study; sepsis/infection
	>30 days post-treatment	163	Disease under Study; sepsis/infection
	>30 days post-treatment	116	unknown

Data Source: Table 3.0165 and Listing 23.1080

Sponsor's table from report for Study ELT112523

Hepatobiliary adverse events were examined as events of special interest. Eltrombopag is metabolized by the liver and can cause liver enzyme elevations and indirect bilirubin elevations due to inhibition of UGT1A1 and inhibition of the transporter OATP1B1. A total of 16 patients had hepatobiliary adverse events. In Study ELT112523 6 subjects had total bilirubin >1.5 x upper limit of normal (ULN), all due to increased indirect bilirubin. No patient had total bilirubin >2 x ULN. Four subjects experienced elevations of ALT or AST >5 xULN; all 4 had elevations at baseline. Two patients (b) (6) had concurrent alanine aminotransferase (AAT) or asparatate aminotransferase (AST) >3 x upper limit of normal (ULN) and total bilirubin >1.5 x ULN. (Increase was due to indirect bilirubin; direct bilirubin ≤25%). For subject (b) (6) elevations were transient and resolved with continued eltrombopag treatment. For subject (b) (6) elevations were noted on Day 85 assessment and followup values were not available. The patient continued on eltrombopag for about 3 additional weeks when she was hospitalized for sepsis and eltrombopag was discontinued. See Dr. Dmytrijuk's Clinical Review for more detailed discussion of the events.

Because development of cytogenetic abnormalities in the bone marrow is a known complication of severe aplastic anemia, testing for cytogenetic abnormalities was done for patients in the study. Of the 43 treated patients, 38 had normal karyotype at study entry, 3 had a baseline abnormality, and samples for 2 were inadequate for the test. Of

the three who had abnormal baseline, 2 had no change during eltrombopag treatment and 1 had normal karyotype on repeated examination during eltrombopag treatment. Of the 40 patients who had normal karyotype or insufficient sample at baseline, 7 had an abnormality at followup as shown in the sponsor's table below for the initial sNDA submission. In the 120-Day Safety update (see below), one additional patient (b) (6) had a cytogenetic abnormality detected (deletion of chromosome 13 with no evidence of dysplasia) at Day 303.

Table 31 Summary of Cytogenetic Abnormalities

Subject ID	Cytogenetic abnormality	Treatment Duration (Months)	Dysplasia	Outcome
(b) (6)	45XY,-7[4]/46XY[16]	3	Baseline: 'dyspoietic maturation' Day 133:'findings are worrisome for hypocellular MDS.'	Died of MDS
	+8[9]/46XX[11] +8[2]/46XX[18]	3 1M post-treatment	No	Referred to transplant
	-7[5]/DER(16)t(1:16)[3]/46/XY[12] DER(16)t(1:16)[4]/46XY[16]	3 1M post-treatment	No	Referred to transplant
	DEL(13)[19]/46XY[1]	13.7	Baseline: 'without clear cut dysplasia' Day 419: 'erythroid dominance, L-shift in erythroid maturation with mild megaloblastic changes & occasional (<5%) ringed sideroblast, progressive but mildly L-shift myeloid maturation, mildly decrease megakaryocytes & without increased blast.'	MDS Received a Transplant
	+21[3]/46XY[17] DEL-7[2]/46XY[19]	3 6M post-treatment	Baseline: 'Erythroid predominance & no increase in blasts' Day 274: 'Markedly decreased megakaryocytes erythroid predominance with mild dyserythropoiesis. Less than 5% blasts'	Referred to transplant
	-7[5]46XY[15]	3	No	Referred to transplant
	+1DER(1:7)[4]/46XY[16] (-7[2]/46XY[18])	3 1M post-treatment	No	MDS[c] Received a Transplant

Data Source: Listings 23.0010, 30.0070, 30.0080, 30.0090
a. Non-responder
b. Bi-lineage responder (platelets and hemoglobin)
c. MDS diagnosis was based solely on cytogenetics.

Sponsor's table from report for Study ELT112523

Three patients were diagnosed with myelodysplastic syndrome (MDS) during the study as shown in the table above. One enrolled patient had a change in diagnosis to MDS before eltrombopag treatment and is not included in the study analysis population. See Dr. Dmytrijuk's review for more detail regarding these patients.

There were no thromboembolic events in the study up to time of data cutoff for the sNDA submission. However, reported in the 120-Day Safety Update, one patient (b) (6) a 45 year old White male with history of PNH clone, developed a proximal deep vein thrombosis (DVT) in the right leg 14 months after discontinuing eltrombopag.

There were no pregnancies during the study.

Safety Results from Other Studies:
The Integrated Summary of Safety (ISS) for the sNDA included safety data from two additional studies. These were ELT116643 [an ongoing supportive study in patients age ≥2 years with SAA who are receiving standard front-line treatment with horse anti-thymocyte globulin and Cyclosporin A (hATG/CsA) in combination with eltrombopag] and PMA112509 [a completed, placebo-controlled study in 98 randomized patients (64 eltrombopag, 34 placebo) with advanced MDS or acute myeloid leukemia (AML) treated with eltrombopag doses up to 300 mg daily]. Available safety results for these are summarized briefly below.

In Study ELT116643 patients are to be treated with eltrombopag and primary efficacy assessment (complete hematologic response) made at 6 months with periodic follow up for 5 years. For the ISS a total of 31 patients had enrolled and 30 had received eltrombopag (included 5 subjects 12-18 years of age). Among these, 18 had completed 6 months of treatment, 8 were ongoing in the study, and 5 had withdrawn (1 who received treatment with hATG/CsA but not eltrombopag due to cytogenetic abnormality detected on baseline bone marrow aspirate; 1 who went to allogeneic bone marrow transplant after ~2 months; 2 who had a cytogenetic change at 3 months [one with deletion in chromosome 13, no dysplasia; one with monosomy 7 and one month later dysplasia and increase blasts in marrow]; and 1 who died before the 3 month assessment due to encephalopathy and respiratory failure). Serious adverse events reported in this study are shown in the following sponsor's table.

Table 6 SAEs in ELT116643

Subjects	Preferred Terms	Relatedness	Outcome
(b) (6)	Idiopathic thrombocytopenic purpura	No	Improved
	Meningitis aseptic	Yes - IVIG	Unknown
	Sinusitis fungal	No	Unresolved
	Haematochezia	Yes - ATG	Resolved
	Gastrointestinal haemorrhage	Yes - ATG	Resolved
	Infection	No	Improved
	Haematoma	No	Unknown
	Abdominal wall haematoma	No	Unresolved
	Pyrexia	No	Unknown
	Squamous cell carcinoma	Yes - Eltrombopag, ATG & CsA	Unknown
	Headache	Yes – CsA	Improved
	Basal cell carcinoma	No	Unknown
	Actinic elastosis	No	Unknown
	Encephalopathy	No	Fatal
	Respiratory failure	No	Fatal
	Cellulitis	No	Unknown
	Tooth abscess	No	Unknown
	Appendicitis	No	Unknown
	Febrile neutropenia	No	Unknown
	Neutropenic infection	No	Unknown
	Hyperkalaemia	Yes – CsA	Unknown

Sponsor's table from ISS in sNDA submission

For the ISS in Study PMA112509 in patients with MDS a total of 95 patients were studied (64 eltrombopag, 34 placebo). The following sponsor's table summarizes adverse events experienced by patients in this study:

Table 23 Overall Summary of Adverse Events Starting On-Treatment in Study PMA112509 (Safety Population)

Subjects with Event	Placebo (N=34)		Eltrombopag (N=64)	
	n (%)	Events	n (%)	Events
Any AE	32 (94)	345	63 (98)	887
Any SAE	22 (65)	50	49 (77)	135
Treatment-related AE	12 (35)	26	36 (56)	79
Treatment-related SAE	3 (9)	4	1 (2)	2
AE leading to withdrawal from study	13 (38)	19	13 (20)	14
SAEs leading to withdrawal from study	11 (32)	15	12 (19)	13

Data Source: PMA112509 CSR Section 6.2

Sponsor's table from ISS in sNDA submission

The most common adverse events in patients who received eltrombopag were pyrexia (42%), nausea (31%), diarrhea (30%) and fatigue (25%).

Other Information:
120-Day Safety Update: The sponsor submitted the 120-Day Safety Update on June 19, 2014 covering the time from data cutoff for the sNDA through March 31, 2014. The report included safety results from ongoing Studies ELT112523 (the ongoing extension of the study discussed above), ELT116643 (a supportive study in patients with SAA who are receiving standard front-line treatment with horse anti-thymocyte globulin and Cyclosporine A (hATG/CsA) in combination with eltrombopag) and ELT116826 (a new study of extended eltrombopag dosing [planned 6 months] in patients ≥2 yrs of age with refractory SAA).

In extension of Study ELT112523 an additional 3 subjects completed 1 year of eltrombopag treatment. The following sponsor's table summarizes the status of patients in ELT112523 as of the March 31, 2014 cutoff date for the 120-Day Safety Update.

Table 3 Summary of Eltrombopag Treatment Status in Study ELT112523

	ISS	Safety Update
	Eltrombopag N=43	Eltrombopag N=43
Treatment Status, n (%)		
Discontinued treatment	37 (86)	39 (91)
Ongoing	6 (14)[a]	4 (9)[a]
Primary Reason for Eltrombopag Treatment Discontinuation[b], n (%)		
Completed scheduled treatment period	22 (51)	22 (51)
Adverse event	5 (12)[c]	5 (12)[c]
Responders tapered off due to continued efficacy	4 (9)	5 (12)
Lack of efficacy	2 (5)	2 (5)
Detection of cytogenetic abnormality	1 (2)	2 (5)
Lost to follow-up	1 (2)	1 (2)
Subject withdrew consent	1 (2)	1 (2)
Investigator discretion	1 (2)	1 (2)

a. One subject (b) (6) interrupted treatment during the extension. After a treatment interruption at the time of the ISS, Subject (b) (6) resumed eltrombopag and continues to receive eltrombopag at the time of this safety update.
b. Subjects can have only 1 primary reason for treatment discontinuation.
c. The primary reason for discontinuation of treatment was reported as an AE for 5 subjects. AEs leading to treatment discontinuation were reported in 4 subjects (Section 3.2.1.3.1). ELT112523 Subject (b) (6) experienced a viral infection that led to treatment discontinuation, but the result of the viral infection was reported as 'dose not changed'.

Sponsor's table from 120-Day Safety Update

The sponsor states that of 10 patients who continue in the study, 4 are still receiving eltrombopag and 5 (1 in addition to the 4 mentioned in the ISS Report) were tapered off eltrombopag due to trilineage hematopoiesis.

In Study ELT116643 a total of 47 patients have been enrolled and 44 have received eltrombopag. One was not treated because of baseline cytogenetic abnormality and two

have been treated with hATG/CsA but not eltrombopag. One subject in Study ELT116643 died of encephalopathy and respiratory failure prior to 3 months evaluation. The sponsor notes that preliminary pharmacokinetic data from this study suggest that subjects with SAA receiving CsA along with eltrombopag have a higher exposure for eltrombopag.

In Study ELT116826, as of March 31, 2014 there were 15 subjects enrolled. Of these 12 were on therapy (4 for >6 months), 1 discontinued at 6 months, and 2 discontinued eltrombopag due to developing a cytogenetic abnormality at 3 months. As of the cutoff date 2 patients had achieved a response (both bilineage) at 3 months and maintained that response at 6 months evaluation. An additional 2 patients had achieved a response (bilineage) at 3 months and had not yet undergone 6 months evaluation. There were no reports of hepatotoxicity, PNH evolution, deaths or development of MDS or AML.

Eltrombopag was first approved for marketing in the U.S. on November 20, 2008 for treatment of thrombocytopenia in patients with chronic idiopathic thrombocytopenia (ITP). Since then it has been approved in a number of countries worldwide. The sponsor estimates worldwide use as approximately (b) (4) patient years. The sponsor reports a total of 4458 spontaneous and postmarketing reports as of March 31, 2014, about 57% from the U.S. The most frequently reported event was 'drug ineffective' (10.5%). Among the events 769 (584 U.S.) had a fatal outcome. The sponsor states that the cause of death was unspecified in 39% of the case and the remaining causes of death pertained primarily to elderly patients with underlying malignancies, infections, cardiac disorders, renal disease, respiratory complications, and nervous system disorders. No new safety findings or concerns were noted.

The 120-Day Safety Update did not reveal new safety concerns for eltrombopag.

Risk Evaluation and Mitigation Strategy (REMS) Program: The original accelerated approval of Promacta on November 20, 2008 for chronic ITP included a REMS program to ensure that the benefits of the drug outweighed the increased risks of hepatotoxicity, bone marrow fibrosis, serious hemorrhage resulting from worsened thrombocytopenia after cessation of eltrombopag, thromboembolic complications, and an increased risk of hematological malignancies and progression of malignancy in patients with a pre-existing hematological malignancy or myelodysplastic syndrome (MDS). Full approval for the ITP indication was granted on February 25, 2011. Evaluation of the additional safety data and REMS review over the years since approval resolved some of the concerns and resulted in REMS modifications. Supplement 013 (S-013) which proposed to eliminate the requirement for the Promacta REMS was approved on July 16, 2014.

Pediatrics: Eltrombopag has been granted Orphan Drug Designation for treatment of aplastic anemia and therefore, the sponsor is exempt from requirement for pediatric studies of Promacta under Pediatric Research Equity Act (PREA). Though SAA occurs in the pediatric population and pediatric patients ≥12 years of age were allowed to

participate in Study ELT112523, only 2 pediatric patients (both 17 years of age) were enrolled.

The sponsor is currently investigating eltrombopag for use in pediatric patients with chronic idiopathic thrombocytopenic purpura (ITP) under a Written Request for Pediatric Studies (originally issued 1/25/2010; amended 11/29/2011).

Discussion:
Efficacy:
In Study ELT112523 a total of 43 patients with severe aplastic anemia (SAA), largely refractory to at least 2 highly immunosuppressive therapy regimens and largely transfusion dependent (platelet and RBC) were treated with eltrombopag starting at 50 mg daily and escalated to maximum of 150 mg daily for a planned total duration of at least 8 weeks. Among these patients 17 (39.5%; 95% CI 25, 56) were able to achieve a treatment response [defined as any one or more of: (1)platelet response defined as platelet count increase to $20x10^9$/L above baseline, or stable platelet count with transfusion independence for a minimum of 8 weeks; (2)erythroid response for subjects with a pretreatment hemoglobin of less than 9 g/dL defined as an increase in hemoglobin by > 1.5g/dL without packed red blood cell (PRBC) transfusion support, or a reduction in the units of transfusions by an absolute number of at least 4 PRBC transfusions for 8 consecutive weeks compared with the pretreatment transfusion number in the previous 8 weeks; or (3)neutrophil response for those with a pretreatment absolute neutrophil count (ANC) of $<0.5 \times 10^9$/L defined as at least a 100% increase or an absolute increase > 0.5×10^9/L]. The limited number of patients who were tapered off eltrombopag due to meeting tri-lineage hematopoiesis criteria appeared to maintain transfusion independence at least for several months off eltrombopag.

The largest number of responders showed a response in platelet counts, consistent with the known effect of eltrombopag in inducing proliferation and differentiation of megakaryocytes via interaction with the thrombopoietin receptor (TPO-R) on megakaryocytes and with observed effectiveness in increasing platelet counts in clinical studies of normal subjects and patients with idiopathic thrombopocytopenic purpura (ITP). Because the TPO-R is also expressed on the surface of hematopoietic cells (HSC) as well as on surface of megakaryocytes and pre-clinical research has shown stimulatory effects of eltrombopag on HSC, a stimulatory effect on hematopoietic cell lines in addition to platelets might also be expected.

Severe aplastic anemia is an uncommon, life-threatening disease with poor outcomes and for which therapeutic options are limited. The overall 39.5% response rate seen in Study ELT112523 in this population of patients with refractory SAA is highly supportive of a meaningful clinical benefit in the patients studied.

Safety: As of March 31, 2014 a total of 105 patients with SAA have received eltrombopag in the sponsor's reported database. In Study ELT112523 which enrolled

and treated 43 patients, most patients escalated to the highest dose (150 mg daily). Fewer than 10% of patient discontinued eltrombopag due to adverse events. The most common adverse events were nausea, fatigue, cough, diarrhea, and headache. There were serious adverse events of febrile neutropenia, sepsis, and viral infection. Though some cytogenetic abnormalities were noted during the studies, some patients had baseline abnormalities and patients with SAA are known to have a higher occurrence of such changes. Only one case of thrombotic event was reported in the database. There were some occurrences of elevated transaminases but no cases of hepatotoxicity. Overall, adverse effects during treatment with eltrombopag in the reported studies in patients with SAA are consistent with the labeled safety profile of the product and with the underlying disease being treated and the safety profile appears acceptable.

Conclusions and Recommendations:
Based on the efficacy and safety results of Study ELT116826 and supportive information from other studies in severe aplastic anemia (SAA) and other populations, the benefit/risk profile for use eltrombopag for treatment of patients with SAA who have had an insufficient response to immunosuppressive therapy is favorable and eltrombopag may be approved for this indication. The recommended dose is 50 mg once daily (25 mg in patients of East Asian ancestry or with hepatic impairment) and dose is adjusted to maintain platelet count $\geq 50 \times 10^9$/L but is not to exceed 150 mg daily. Safety concerns are as for the currently approved indications and include hepatotoxicity and possible thrombotic/thromboembolic complications. Increased development of cytogenetic abnormalities is associated with SAA and a few cases of cytogenetic changes were reported in the study and should be mentioned in the labeling.

I have no recommendations for REMS. The sponsor should be encouraged to complete and submit the final reports for ongoing Studies ELT116643 and ELT116826 when they become available.

Eltrombopag has been granted Orphan Designation for treatment of aplastic anemia and therefore, requirements for Pediatric Research Equity Act (PREA) do not apply.

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/s/

KATHY M ROBIE SUH
08/22/2014

CLINICAL REVIEW

Application Type	Efficacy Supplement
Application Number	22-291 Supplement 12 Supporting Document 456
Priority or Standard	Priority
Submit Date	February 27, 2014
Received Date	February 27, 2014
PDUFA Goal Date	August 27, 2014
Division / Office	Division of Hematology Products
Reviewer Name	Andrew Dmytrijuk, M.D.
Review Completion Date	August 14, 2014
Established Name	Eltrombopag
Trade Name	Promacta
Therapeutic Class	Thrombopoietin Receptor Agonist
Applicant	GlaxoSmithKline One Franklin Plaza Philadelphia, PA 19102
Formulation	Oral
Dosing Regimen	50 mg Once Daily
Indication	Treatment of Cytopenias in Patients with Severe Aplastic Anemia (SAA) Who Have Had an Insufficient Response to Immunosuppressive Therapy (IST)
Intended Population	Patients with SAA

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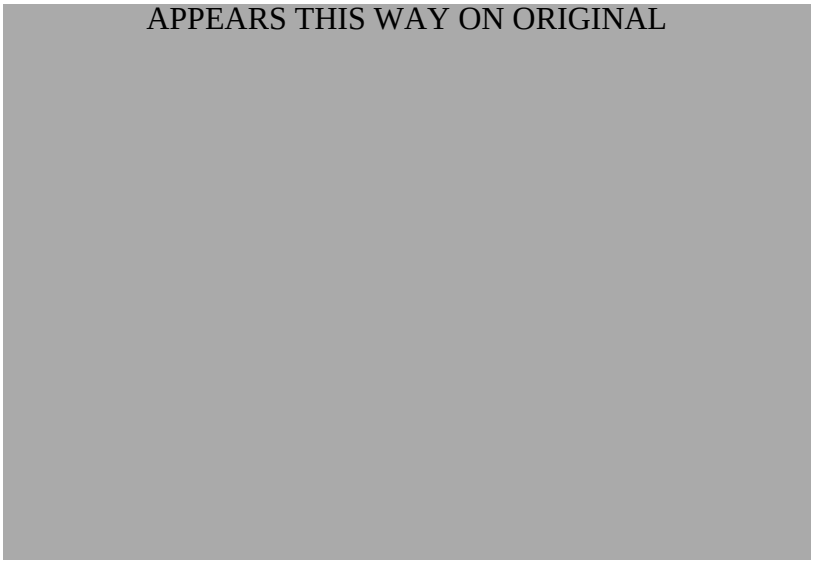


ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATG	Anti-thymocyte globulin
AUC	Area under the curve
CBC	Complete blood count
CI	Confidence interval
CR	Complete hematologic response
CsA	Cyclosporine A
CSR	Clinical study report
EPO	Erythropoietin
FDA	Food and Drug Administration
GSK	Glaxo Smith Kline
hATG	Horse anti-thymocyte globulin
HCV	Hepatitis C virus
HSPC	Hematopoietic stem and progenitor cells
HSCT	Hematopoietic stem cell transplant
IND	Investigational new drug
ISS	Integrated Summary of Safety
IST	Immunosuppressive therapy
ITP	Immune thrombocytopenic purpura
MDS	Myelodysplastic syndrome
NA	Not applicable
NHLBI	National Heart Lung Blood Institute
NIH	National Institutes of Health
PR	Partial hematologic response
rATG	Rabbit ATG
RBC	Red blood cell
SAA	Severe aplastic anemia
SAE	Serious adverse event
TPO	Thrombopoietin
TPO-R	TPO receptor
ULN	Upper limit or normal

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The efficacy supplement is approvable for the treatment of patients with severe aplastic anemia (SAA) who have had an insufficient response to immunosuppressive therapy (IST).

The sponsor's proposed indication is as follows:

- Promacta is a thrombopoietin receptor agonist indicated for the treatment of cytopenias in patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.

See also section 9.3 Labeling Recommendations in this review.

1.2 Benefit/Risk Assessment

ELT112523 was the primary study used to support the safety and efficacy of eltrombopag for the treatment of patients with SAA who had an insufficient response to IST. ELT112523 was a single arm, single center, open label study which enrolled 43 patients with SAA who had an insufficient response to at least one prior IST and who had a platelet count ≤30,000/μL. In this study patients had median age of 45 years (range 17-77 years) and 24/43 (56%) were male. In this study 36/43 (84%) of patients had received ≥ 2 prior ISTs. At baseline, the median platelet count was 20,000/μL (range 6000-90,000/μL), the median hemoglobin level was 8.4 g/dL (range 6.6-13.8 g/dL), the absolute neutrophil count (ANC) was 580/μL (range 7-2810/μL). In the study, 35/43 (81%) patients required transfusions of platelets and red blood cells (RBCs) at baseline. In the study the median duration of therapy with eltrombopag was 3.6 months (range 2-37months). There were 33/43 (77%) of patients who were treated with eltrombopag for ≥3 months, 11/43 (26%) of patients who were treated with eltrombopag for ≥ 6 months and 7/43 (16%) of patients who were treated with eltrombopag for ≥ 12 months.

In ELT112523 eltrombopag was administered at an initial dose of 50 mg once daily for 2 weeks and was increased every 2 weeks up to a maximum dose of 150 mg once daily. The dose of eltrombopag was adjusted based on platelet counts with the goal to maintain the platelet count in the ≥ 50,000/μL-<200,000/μL range. Eltrombopag was discontinued after 16 weeks of therapy if no hematologic response was observed. The primary endpoint of study ELT112523 was hematologic response assessed after 12 weeks of treatment with eltrombopag. Hematologic response was defined as meeting one or more of the following criteria:

- Platelet count increases to >20,000/μL above baseline, or stable platelet counts with transfusion independence for a minimum of 8 consecutive weeks.
- Hemoglobin increase by ≥1.5g/dL, or a reduction in ≥4 units of red blood cell (RBC) transfusions for 8 consecutive weeks.
- ANC increase of 100% (pre-treatment levels < 500/μL) or an ANC increase > 500/μL at least once.

In ELT112523, 17/43 patients (40%, 95% CI = 25-56) achieved a hematologic response. Bi-lineage or tri-lineage responses were observed in 4/17 (24%) of the responders. The median platelet transfusion free period was 200 days (range 8-1096 days) and the median RBC transfusion free period was 208 days (range 1082 days).

There were 33/43 (77%) of patients treated for ≥ 3 months and 7/43 (16%) of patients treated for > 12 months and 27/40 patients (63%) received the maximum protocol allowed eltrombopag dose of 150mg orally once daily. In ELT112523 the most common adverse events (AEs) occurring in ≥20% of patients were nausea, fatigue, cough, diarrhea and headache. The most common serious adverse events (SAEs) occurring in ≥ 5% patients were febrile neutropenia, sepsis and viral infection. There were 6 deaths reported during the study. There were no subjects who died while receiving eltrombopag therapy. There were 2 patients who died within 30 days of the last dose of eltrombopag (both deaths related to sepsis) and 4 patients died > 100 days after the last dose of eltrombopag (2 deaths due to sepsis, 1 AML (patient ID (b) (6)) and 1 cause of death was unknown but occurred 116 days from the last dose of eltrombopag). Patient (b) (6) was on eltrombopag therapy for a period of 3 months and was noted to have abnormal hematopoietic maturation at baseline. There were no thromboembolic AEs reported. There were few (n = 6) patients with hepatobiliary AEs (elevated serum liver transaminases) of grade 3 and there were no grade 4 elevations in liver transaminases. There were no grade 3 or 4 elevations in total bilirubin.

Severe aplastic anemia (SAA) is a very rare, life-threatening, acquired bone marrow failure disease characterized by tri-lineage marrow hypoplasia and a lack of hematopoietic stem and progenitor cells due to an immune-mediated attack on the bone marrow. The annual incidence of aplastic anemia is 2 cases per million population in the United States. (Biswajit 2012) Management of these patients is challenging and outcomes are poor and approximately 40% of IST-refractory SAA patients die of bleeding or infection within 5 years of diagnosis. No established standard of care exists for immunosuppressive therapy (IST)-refractory SAA patients who lack a suitable donor for hematopoietic stem cell transplant (HSCT), other than transfusion support and treatment of infections. In addition, hematopoietic stem cell transplant for this disease is generally limited to those patients under the age of 45 who are in good health. In one report, from January 1978 to December 2001, 133 patients with severe aplastic anemia (SAA) underwent non-T cell-depleted allogeneic bone marrow transplantation from an HLA-identical sibling donor, at the Hospital Saint Louis, using either the combination of cyclophosphamide (Cy) and thoracoabdominal irradiation (TAI; n = 100) or Cy and

antithymocyte globulin (ATG; n = 33) as a conditioning regimen. With 13.6 years of follow-up, the 10-year survival estimate was 64%. The authors state that four factors were associated with lower survival: older age, use of Cy-TAI, treatment with androgens or IST prior to transplantation and grade II to IV acute graft-versus-host disease (aGvHD). (Ades 2004). Eltrombopag may offer another therapeutic option for patients with SAA which could allow patients time to find a donor and undergo a hematopoietic stem cell transplant.

Other therapies for SAA include anti-thymocyte globulin (ATG), high dose corticosteroids, cyclosporine, mycophenolate mofetil and cyclophosphamide. (Lichtman 2003) However, these therapies are generally poorly tolerated, require hospitalization and close patient monitoring, and have limited success in those with relapsed or refractory disease.

The benefit/risk assessment for eltrombopag for the proposed indication favors the approval of eltrombopag. Although study ELT112523 was a small study this could be expected due to the rarity of the disease being studied. All patients were enrolled and treated at a single center, i.e., the National Institutes of Health which has internationally recognized expertise in the treatment of patients with SAA. The study was initiated on June 23, 2009 and the data cutoff date was June 1, 2013. In study ELT112523 in patients with SAA who had insufficient responses to prior IST there were 17/43 (40%) patients who responded to eltrombopag therapy and 4/43 patients who had multi-lineage hematologic responses. Overall, therapy with eltrombopag resulted in adverse events that were similar to those in the current eltrombopag product label in terms of grade and frequency.

There was no clear evidence that eltrombopag had a causative effect on cytogenetic abnormalities reported during the study. In SAA there is generally a high rate of background rate of cytogenetic abnormalities in patients with SAA. In aplastic anemia 4-15% of patients have baseline abnormal cytogenetics. (Gupta 2006) In one study 69 patients with acquired severe aplastic anemia underwent cytogenetic examination of bone marrow cells at the time of diagnosis and after IST. IST consisted of anti-lymphocyte globulin (ALG) with or without corticosteroids in 40 patients, 8 were treated only with corticosteroids and 21 were treated with the combination of ALG plus cyclosporine plus corticosteroids. In this study 51/69 (74%) of patients with normal cytogenetics at baseline had normal cytogenetics after IST. There were 7/69 (10%) of patients who had a normal baseline cytogenetic evaluation and subsequently at least one abnormal cytogenetic analysis after IST. There were 3/69 (4%) of patients who had a baseline abnormal cytogenetic evaluation which remained abnormal after IST. There were 8/69 (12%) of patients with an abnormal baseline in which the cytogenetics reversed to normal after IST. The most frequent abnormality was trisomy 8 (n = 8) followed by monosomy 7 (n = 2). In this study 3 patients developed acute leukemia of which 2 patients had baseline normal cytogenetic and subsequent abnormal cytogenetics after IST and 1 patient had baseline abnormal cytogenetics which

remained abnormal after IST. (Mikhailova 1996) Similarly, in ELT112523 there were 6/43 (14%) of patients who had a baseline normal cytogenetic evaluation followed by an abnormal cytogenetic evaluation after eltrombopag therapy. The baseline cytogenetic sample was not adequate for evaluation in one patient. There were 5 patients who had complex changes in chromosome 7. One patient died due to myelodysplastic syndrome/acute myeloid leukemia. Two other patients received bone marrow transplants. Deaths that were reported in study ELT1123 were primarily due to sepsis which can be expected in this generally neutropenic patient population.

Although study ELT112523 is a small (n = 43), single arm study it provides convincing evidence that eltrombopag therapy can increase blood counts (platelets, hemoglobin or white blood cells) in patients with IST-refractory SAA. The small number of patients enrolled in the study can be expected due to the rarity of the disease. In addition, current treatment options including hematopoietic stem cell transplant for patients with SAA, with the exception of supportive care options, are immunosuppressive which increase the risk for infections. Thus, there is an unmet need for other therapies which do not increase the risk of infection and are well tolerated. In contrast to IST therapies, eltrombopag appears to stimulate hematopoiesis, which offers a mechanistically new treatment option for patients with SAA who are refractory to IST. Also, about a quarter of patients with severe aplastic anemia remain pancytopenic despite immunosuppressive therapy. (Desmond, 2014) As noted in ELT112513 40% of patients responded to eltrombopag therapy and approximately 10% of patients in this study had a tri-lineage response.

The current product label states that eltrombopag interacts with the transmembrane domain of the thrombopoietin (TPO) receptor (also known as cMpl) leading to increased platelet production. The effect of eltrombopag to increase platelet counts has been observed in numerous patients with immune thrombocytopenic purpura, in patients undergoing therapy for chronic hepatitis C virus (HCV) infection, in patients undergoing chemotherapy (Chawla 2013) and in normal healthy volunteers as well. It can be expected that eltrombopag would have a similar effect on patients with severe aplastic anemia because the mechanism of TPO is the same regardless of the disease. Patients with SAA often require platelet and other blood product transfusion support. The effect of eltrombopag to increase platelet counts and potentially decrease the frequency of transfusions would be beneficial. In ELT112523, among the 17 responders, there were 8 patients who had a response based on stable platelet counts with transfusion independence for a minimum of 8 consecutive weeks. Of these 8 patients, there were 3 patients who had a response in platelet counts as well, i.e., they had a platelet count increase > 20,000/μL above baseline.

1.3 Recommendations for Postmarketing Risk Evaluation and Mitigation Strategies

I do not recommend a postmarketing Risk Evaluation and Mitigation Strategy (REMS) program for this new indication in SAA.

1.4 Recommendations for Postmarketing Requirements and Commitments

I recommend that the sponsor complete and submit for review the ongoing study ELT116643 titled, "Eltrombopag Added to Standard Immunosuppression in Treatment Naïve Severe Aplastic Anemia" as a Post-Marketing Commitment (PMC). Briefly, this study is a phase1/2, open-label, single arm, single-center study of eltrombopag administered in combination with ATG and cyclosporine. In this study the sponsor plans to enroll up to 62 patients with SAA who are age ≥ 2 years. Patients are to receive eltrombopag orally once daily, starting at 150mg in patients age 12-85 years, 75mg for patients age 6-11 years and 2.5mg/kg for patients age 2-5 years on day 14 after the start of IST to avoid overlap with the known transient hepatotoxicities associated with IST. The starting dose of eltrombopag will be reduced by 50% in patients of East-Asian ancestry. The planned duration of therapy with eltrombopag is 6 months. The dosing of eltrombopag will be adjusted for toxicities according to the approved eltrombopag label and to maintain platelet counts < 200,000/μL. The primary efficacy endpoint is the rate of complete hematologic response at six months of therapy. Serial blood counts will be obtained. A complete response will be defined as meeting the following criteria, i.e., ANC > 500/μL, Hgb level increase by > 1.5g/dL and platelet count > 20,000/μL based on 2 serial blood counts at least one week apart. Peripheral blood smears will be evaluated for histologic abnormalities and bone marrow biopsies will be performed at landmark time points of 3 months and 6 months after therapy. The primary efficacy endpoint and AEs will be described descriptively. This study was initiated June 14, 2012 and has an expected completion date of May 2015.

I do not recommend any new postmarketing requirements based on the results of the study ELT112523. Also, SAA is a very rare disease which would make enrollment into large postmarketing trials difficult.

Orphan Drug Designation for the proposed indication, i.e., for the treatment of cytopenias in patients with severe aplastic anemia (SAA) who have had an insufficient response to immunosuppressive therapy (IST), was granted on November 8, 2013.

2 Introduction and Regulatory Background

2.1 Product Information

Eltrombopag is a synthesized thrombopoietin (TPO) receptor which is administered orally. The proposed mechanism of action is that eltrombopag interacts with the transmembrane domain of the TPO receptor (also known as cMPL). This leads to increased platelet production by megakaryocytes in the bone marrow.

Eltrombopag received accelerated approval on November 20, 2008 and subsequent full approval on February 25, 2011 for the treatment of thrombocytopenia in patients with chronic immune thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulin therapy, or splenectomy. Also, eltrombopag was approved on November 16, 2012 for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow initiation and maintenance of interferon-based therapy.

2.2 Tables of Currently Available Treatments for Proposed Indications

There is currently no FDA approved therapy for the treatment of cytopenias in patients with SAA who have had an insufficient response to IST. Therapies currently used for the treatment of SAA consist of

- Supportive care
- Hematopoietic stem cell transplant
- Rabbit or horse ATG
- High dose corticosteroids
- Cyclosporine
- Mycophenolate mofetil
- Cyclophosphamide

2.3 Availability of Proposed Active Ingredient in the United States

Eltrombopag (Promacta®) is currently marketed in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

The eltrombopag product label has a boxed warning which states there is a risk for hepatic decompensation in patients with chronic hepatitis C, i.e., in patients with chronic hepatitis C, eltrombopag in combination with interferon and ribavirin may increase the risk of hepatic decompensation.

The eltrombopag product label states in the Warnings and Precautions Section that eltrombopag can cause liver enzyme elevations. Eltrombopag inhibits the UGT1A1 and OATP1B1 hepatic enzymes, which may lead to indirect hyperbilirubinemia. If bilirubin is elevated, the product label states to perform fractionation. Patients should be evaluated with repeat serum liver tests within 3 to 5 days if an elevated bilirubin is detected. Eltrombopag should be discontinued if alanine aminotransferase (ALT) levels increase to ≥ 3X ULN in patients with normal baseline liver function or ≥ to 3X baseline in patients with pre-treatment elevations in transaminases that are:

- Progressively increasing
- Persistent for ≥4 weeks
- Accompanied by increased direct bilirubin
- Accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation.

The Warnings and Precaution section states that there is a risk of thrombotic or thromboembolic complications with eltrombopag therapy. Thrombotic/thromboembolic complications may result from increases in platelet counts with eltrombopag. The product label states that thrombotic/thromboembolic complications included both venous and arterial events and were observed at low and at normal platelet counts. In order to minimize the risk of thrombotic/thromboembolic complications the product label recommends that prescribes do not use eltrombopag in an attempt to normalize platelet counts.

The eltrombopag product label states in the Warnings and Precaution Section that there is a risk of cataracts. The product label recommends that patients should have baseline ocular examination and regular ocular examinations during therapy with eltrombopag.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

- Accelerated Approval - November 20, 2008 for ITP.
- Conversion to Full Approval - February 25, 2011.
- Full Approval - November 19, 2012 for chronic hepatitis C indication.
- SAA Guidance Meeting with sponsor - September 19, 2012.
- SAA Pre-sNDA Meeting with sponsor - May 13, 2013. During this meeting a recommendation was made by the Division of Hematology Products (DHP) that evidence for durability of response for eltrombopag would be needed in order to establish clinical benefit. In addition, it was recommended by DHP that a hematologic response of at least 6 months would more likely allow assessment of clinical benefit.
- SAA Breakthrough Therapy Designation - January 27, 2014.
- SAA Orphan Drug Designation - November 8, 2013.

- SAA Filing Review Meeting - April 16, 2014. A priority review for the proposed indication was granted.

Reviewer comment for section 2: Eltrombopag is marketed in the United States. There are no changes to the eltrombopag background information with the current submission.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

In the current submission the sponsor submitted the ELT112523 study report and case narratives for serious adverse events (SAEs), deaths, and targeted adverse events and data tables. In addition, other key pieces of the submission include an Integrated Summary of Safety (ISS) and a summary report of the post-marketing experience with eltrombopag.

On April 28, 2014 the Office of Scientific Investigations (OSI) was consulted to evaluate 1 study site (Dr. Ronan Desmond, Principal Investigator, National Institutes of Health Department of Laboratory Medicine, 9000 Rockville Pike, Building 10, Bethesda, MD 20892). This study site enrolled all 43 patients included in study ELT112523. A Clinical Inspection Summary consult review was completed by Dr. Anthony Orencia (DSI Reviewer in the Office of Scientific Investigations, final signature date July 21, 2014). In his review Dr. Orencia states that the regulatory classification for the clinical study site is No Action Indicated (NAI). The study data collected from this clinical site appears reliable in support of the requested indication.

3.2 Compliance with Good Clinical Practices

All studies were conducted in compliance with the Declaration of Helsinki, International Conference on Harmonization Guidelines for Good Clinical Practices and local regulatory requirements. The protocols and any amendments were approved by an Institutional Review Board prior to initiation and implementation of these studies and changes. Written informed consent provided by the patient was required and written consent forms for the studies supporting this efficacy supplement were reviewed.

3.3 Financial Disclosures

There were no notable financial disclosures for this application. There were no reports of any Significant Payments of Other Sorts or Proprietary Interests in this application.

Reviewer comment for section 3: The ethical and good clinical practices considerations for this application appear to be acceptable. The OSI review of the one clinical study site is in progress.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There are no changes to the chemistry, manufacturing and controls for Eltrombopag.

4.2 Clinical Microbiology

There are no changes in the clinical microbiology for Eltrombopag.

4.3 Preclinical Pharmacology/Toxicology

There are no changes in the preclinical pharmacology/toxicology for eltrombopag.

4.4 Clinical Pharmacology

Dr. Joseph Grillo (Clinical Pharmacology Reviewer) in his review of NDA 22291 Supplement 12 (final signature date August 1, 2014) stated pharmacokinetic sampling was not collected in this trial. In addition, the applicant did not submit any other clinical pharmacology related information or analyses in this application. The applicant did propose several grammatical changes to section 12.3 (Pharmacokinetics) of the approved labeling (i.e., changed (b) (4) to " compared with" throughout the section (6 instances) and replaced (b) (4) with parentheses in one instance). There are no changes in the clinical pharmacology for eltrombopag.

Reviewer comment for section 4: The efficacy and safety considerations related to other review disciplines appear to be acceptable. A starting dose of 50mg orally once daily was used as the starting dose for ELT112523. A maximum dose of 150mg orally once daily is proposed. Eltrombopag dose modifications are proposed for patients of East-Asian ancestry which are the same as those proposed in the other eltrombopag indications.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The following table shows the clinical study used to support this efficacy supplement.

Table 1. Clinical Study

ELT112523	Efficacy, Safety	OL, NR	Subjects with SAA and thrombocytopenia	Eltrombopag 50mg starting dose (25mg for East Asian subjects), increase by 25mg every 2 weeks dependent on platelet response to a maximum dose of 150mg (75 mg for Asian subjects)	44	Enrolment complete/ ongoing treatment with final CSR

Sponsor's table Module 5.2 page 22

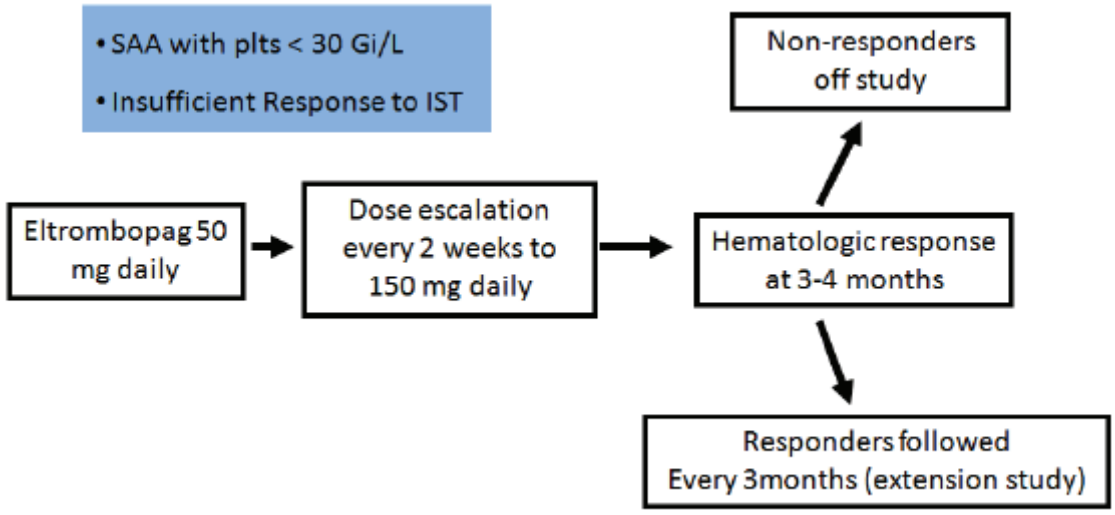
5.2 Review Strategy

The medical review of study ELT112523 titled, "A Pilot Study of a Thrombopoietin-Receptor Agonist (TPO-R Agonist) Eltrombopag in Aplastic Anemia Patients with Immunosuppressive-Therapy Refractory Thrombocytopenia" which was used to support the safety and efficacy of eltrombopag is included in this document.

5.3 Discussion of Individual Studies/Clinical Trials

Briefly, ELT112523 was a phase 2, open label, single center, non-randomized study of eltrombopag therapy for the treatment of cytopenias in patients with SAA who were refractory to IST. The figure below shows the sponsor's study design:

Figure 1. Study Design



Sponsor's figure Module 5.3.5.2 ELT112523 Study Report page 14

SAA was defined according to Rosenfeld et. al. 2003 as follows:

- Bone marrow cellularity of less than 30% and depression of at least 2 of 3 hematopoietic lineages. Bone marrow aspirate and biopsy with cytogenetic analysis was done at study entry and repeated at the 3- to 4-month response

assessment. Bone marrows were also assessed for reticulin formation or fibrosis prior to therapy and at the month 3-4 assessment time point.
- ANC of ≤ 500/μL.
- Absolute reticulocyte count of ≤ 60,000/μL

The primary objective was to assess the safety and efficacy of the oral thrombopoietin receptor agonist (TPO-R) eltrombopag in SAA patients with immunosuppressive-therapy refractory thrombocytopenia. In this study 43 patients age ≥ 12 years with thrombocytopenia (platelet counts ≤ 30,000/μL) diagnosed with SAA who had an insufficient response to at least one prior IST were enrolled. Concurrent stable treatment with cyclosporine was allowed but there were no patients enrolled who were concomitantly treated with cyclosporine. The key exclusion criteria were as follows:

- Diagnosis of Fanconi anemia.
- Infection not adequately responding to appropriate antibiotic therapy.
- PNH with clone size in neutrophils of ≥50%.
- HIV positive.
- Serum creatinine >2.5 mg/dL
- Serum total bilirubin >2.0mg/dL
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 times the upper limit of normal (ULN).
- Treatment with horse or rabbit ATG or alemtuzumab within 6 months of study entry.
- History of arterial or venous thrombosis within 1 year of study enrollment.

The starting dose of eltrombopag was 50mg orally once daily for 2 weeks and increased over 2 week periods up to a maximum dose of 150 mg orally once daily. The dose of eltrombopag was increased by 25 mg every 2 weeks dependent upon platelet response shown in the sponsor's table below.

Table 2. Eltrombopag Dose Adjustment

Platelet Count	Dose Adjustment or Response
<20 Gi/L above baseline or platelet transfusion requirement had not decreased following at least 2 weeks of eltrombopag	Increase daily dose every 2 weeks (+/- 3 days) to maximum 150 mg/day for non- East Asians (75 mg for East Asians).
≥20 Gi/L above baseline but ≤100 Gi/L following at least 2 weeks of eltrombopag	Keep at current dosage.
>100 Gi/L (untransfused) at any time on study	Decrease dosage every 2 weeks (+/- 3 days) to lowest dosage that maintained platelet count ≥20 Gi/L above baseline.
>200 Gi/L (untransfused) at any time on study	Discontinue eltrombopag for one week, if platelets <50 Gi/L; restart at 25 mg, or next lowest dose

Sponsor's table Module 5.3.5.2 ELT112523 Study Report page 20

The dose of eltrombopag was tapered over 16 weeks in those patients who achieved a response and entered into the extension part of the study defined as platelets >50,000/μL, hemoglobin level >10g/dL (in the absence of RBC transfusions) and neutrophils >1,000/μL for more than 8 weeks without transfusion support. The maximum dose of eltrombopag was 150 mg orally once daily and in the East-Asian population the maximum dose was 75 mg orally once daily. Eltrombopag was discontinued after 16 weeks if no hematologic response was observed. Any patients who responded to eltrombopag therapy could continue therapy in an extension phase of the trial. Patients could remain in the extension phase of the study as long as they maintained a treatment response. The dosing of eltrombopag in the extension phase of the trial was carried over from the first part of the study.

The primary endpoint was hematologic response and was assessed after 12 weeks of treatment with eltrombopag. Hematologic response was defined as meeting 1 or more of the following criteria:

- Platelet count increases > 20,000/μL above baseline, or stable platelet counts with transfusion independence for a minimum of 8 consecutive weeks.
- Hemoglobin level increase by > 1.5g/dL, or a reduction in ≥ 4 units of RBC transfusions for 8 consecutive weeks.

- ANC increase of 100% or an ANC increase >greater than 500/μL for 8 consecutive weeks.

The primary safety endpoint was measured using the NCI-CTCAE v.3.0. All patients were to be evaluated at the National Institutes of Health (NIH) at baseline and Weeks 5, 9 and 13. Patients who responded to eltrombopag therapy and entered the extension part of the study were monitored at the NIH every 3 months. After discontinuation of eltrombopag, patients completed follow-up visits at Week 4 and 6 months. Patients may have had additional assessments at the NIH or at their referring home health care provider. Patients were assessed and monitored according to the following schedule:

Table 3. Study Schedule

	SCREEN	ON STUDY MEDICATION												EXTENDED ACCESS			End of study	
PROTOCOL TIMEPOINT		1 WK	2 WKS	3 WKS	4 WKS	5 WKS	6 WKS	7 WKS	8 WKS	9 WKS	10 WKS	11 WKS	12 WKS	6 Mos	9 Mos	12 Mos	30 days	6 mos
DATE		1/1/09	1/8/09	1/15/09	1/22/09	1/29/09	2/5/09	2/12/09	2/19/09	2/26/09	3/5/09	3/12/09	3/19/09	4/16/09	9/17/09	12/14/09	s/p	s/p
Visit location		NIH	HOME	HOME	NIH	HOME	HOME	HOME	NIH	HOME	HOME	HOME	NIH	NIH	NIH	NIH	home/NIH	NIH
Window		± 4days	± 4days	± 4days	± 4days	± 4days	± 4days	± 4days	± 4days	± 4days	± 4days	± 4days	± 7days	±7days	±7days	±7days	last dose	last dose
Actual Day																	drug	drug
REGISTRATION																		
Screening consent																		
Eligibility Criteria																		
Consent																		
Consent documented in med record																		
TREATMENT																		
eltrombopag (daily dosing, dose varies)		Daily	Daily	Daily	Daily	Daily	Daily	Daily	Daily	Daily	Daily	Daily	Daily	Daily	Daily	Daily	None	None
EVALUATIONS																		
H&P or clinical assessment																		
Concurrent medication review																		
LABORATORY MEASURES *repeat within 72 hrs of 1st dose of drug																		
CBC with differential	*																	
Chem 20 (home MD: electrolytes, LFTs, BUN, creat, T bilil)	*																	
Reticulocyte count (home only if available)	*																	
Serum thrombopoietin level																		
Coagulation screen (PT, PTT)																		
Thyroid function tests																		
Folate, B12																		
Iron panel: ferritin, transferrin, % saturation																		
Pregnancy test	*																	
Antibody Screens																		
HIV																		
HBV																		
HCV																		
HSV																		
CMV																		
EBV																		
Peripheral blood smear																		
DAT (as clinically indicated)																		
Type and screen (as clinicaly indicated)																		
HLA typing (if not already avail.)																		
DISEASE MONITORING																		
Bone Marrow Aspirate and biopsy																		
Cytogenetics																		
Flow cytometry of peripheral blood for GPI																		
Other Assessments																		
Quality of Life SF36 (≥18 yrs old only), within 72 hrs of 1st dose of study drug																		
Imaging studies (only if medically indicated)																		
Eye exam for cataracts	add													add		add		add
RESEARCH LABS																		
Research labs draws(NIH visits only)	10cc	10cc			10cc				10cc				10cc	10cc	10cc	10cc	10cc	10cc

Sponsor's table Module 5.3.5.2 ELT112523 Protocol page 51

Reviewer comment for section 5: ELT112523 was the primary study used to support the safety and efficacy of eltrombopag for the treatment of cytopenias in patients with SAA who had an insufficient response to IST. Although the study is not controlled it is reasonably well designed to demonstrate the efficacy and safety of eltrombopag for the proposed indication because of the rarity of the disease and because it would be very unusual for patients with SAA to have improvement in hematologic parameters without effective treatment for the disease. SAA is a chronic disease. In most cases spontaneous remission of aplastic anemia is associated with external factors such drugs or infections. (Lee 2001) In addition, although the study is small the number of patients (n = 43) enrolled into the study is reasonable given the rarity of the disease. Patients were closely monitored for response and AEs. The definition of response was similar to that previously published. (Rosenfeld 2003)

Preclinical studies have shown that eltrombopag can expand human CD34+ CD38-, CD34+ and CD41+ cells, which are hematopoietic stem cells (HSCs) and hematopoietic progenitor cells (HPCs) via phosphorylation of STAT5. (Sun 2012) The authors state that eltrombopag enhanced expansion of HSCs/HPCs of human umbilical cord blood (UCB) in vivo and in vitro, and promoted multi-lineage hematopoiesis through the expansion of bone marrow HSCs/HPCs of human UCB in vivo. The effect of eltrombopag to increase platelet counts has been observed in numerous patients with immune thrombocytopenic purpura, in patients undergoing therapy for chronic hepatitis C virus (HCV) infection, in patients undergoing chemotherapy (Chawla 2013) and in normal healthy volunteers as well. It can be expected that eltrombopag would have a similar effect on hematopoiesis generally and on platelet production in particular in patients with severe aplastic anemia because the mechanism of TPO is similar regardless of the disease.

6 Review of Efficacy

6.1 Indication

The proposed indication is Eltrombopag (Promacta®) is indicated for the treatment of cytopenias in patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.

6.1.1 Methods

The primary endpoint was hematologic response and was assessed after 12 weeks of treatment with eltrombopag. Hematologic response was defined as meeting 1 or more of the following criteria:

- Platelet count increases > 20,000/μL above baseline, or stable platelet counts with transfusion independence for a minimum of 8 consecutive weeks.

- Hemoglobin level increase by > 1.5g/dL, or a reduction in ≥ 4 units of RBC transfusions for 8 consecutive weeks.
- ANC increase of 100% or an ANC increase >greater than 500/μL for 8 consecutive weeks.

In addition the secondary endpoints that were assessed included the number of patients who had a relapse of their disease, clinical laboratory results, the number of transfusions and duration of transfusion-free independence was analyzed. The maximum duration of platelet transfusion independence was defined as the time between transfusions while on treatment, including the time between the first dose of treatment and the first transfusion, and the time between the last transfusion and the last dose of treatment or the last date of contact for subjects still on treatment. RBC transfusion independence was summarized similarly.

6.1.2 Demographics

The demographics of patients in the study are shown in the table below. The table shows that patients enrolled in this study were had a high number of previous ISTs. There were generally similar numbers of male and female patients enrolled. Also, although patients age >12 years were eligible, no patients younger than 17 years actually enrolled. In addition, the table below shows that in this study 36/43 (84%) of patients received ≥ 2 prior ISTs. The median time from diagnosis to study enrollment was 31 months (range 10-190 months).

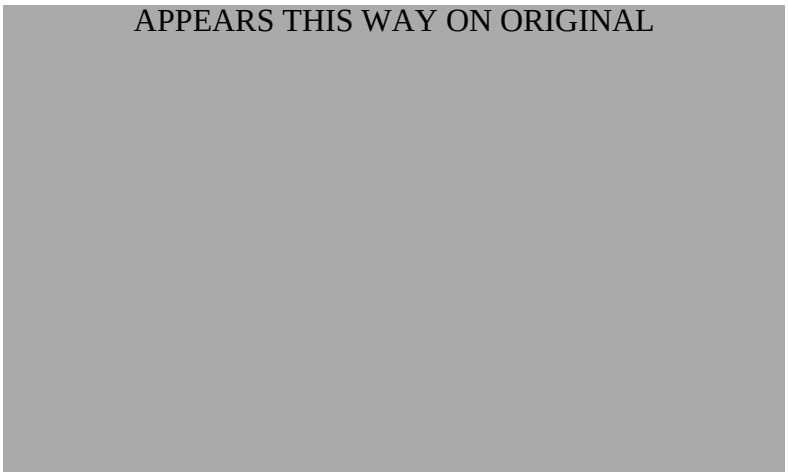


Table 4. Demographics ELT112523

	Eltrombopag (n=43)
Age: Median (Min-Max), years	45 (17-77)
Gender: Male, n (%)	24 (56)
Race: n (%)	
White	20 (47)
Asian	1 (2)
Other	22 (51)
Prior IST	43
Horse ATG	41
≥ 2 Prior IST	36
Abnormal Karyotype	3
Transfusion dependence Red Blood Cells, %	86
Transfusion dependence Platelets, %	91
Median Baseline Level	
Platelets/µL	20,000
Hemoglobin, g/dL	8.4
Absolute Neutrophil Count/µL	580
Median time since diagnosis (Min-Max), months	31 (10-190)

Derived from Sponsor's table Module 5.3.5.2 ELT112523 Study Report page 35-38 and table DM.xpt

6.1.3 Subject Disposition

There were 43 patients who were treated in the study and evaluated for safety and efficacy. There was one patient who was enrolled but was not subsequently treated with eltrombopag due to a baseline diagnosis of myelodysplastic syndrome (MDS). There were 6/43 patients (14%) who remained on study therapy at the time of the data cut off, i.e., June 1, 2013 due to continued response to eltrombopag therapy. There were 4/43 patients (9%) who were tapered off of eltrombopag therapy due to sustained hematologic response. There were 22/43 patients (51%) who completed the scheduled treatment period. The remaining patients, 11/43 (26%) patients were discontinued from the study due to adverse event (n = 5), lack of efficacy (n = 2), detection of cytogenetic abnormality (n = 1), lost to follow-up (n = 1), subject withdrawal of consent not due to adverse event (n = 1), investigator discretion (n = 1).

6.1.4 Analysis of the Primary Endpoint

A total of 17/43 patients (40%) met the hematologic response criteria in at least one lineage at the 12-16 week assessment time point. There was one patient (Patient (b) (6)) who had a tri-lineage hematologic response and 3 patients (Patients (b) (6)) who had bi-lineage responses of the platelets and neutrophils. No other combination of bi-lineage responses in the blood cell lines was observed in this study. There were 13 patients who had a response in one blood cell lineage. The median time to initial response was 12 weeks (range, 8-14 weeks).

6.1.5 Analysis of Secondary Endpoints

In ELT112523, among the 13 patients who had a response in one blood cell lineage, there were 7 patients who had a platelet response, 4 patients who had a neutrophil response and 2 patients had a red blood cell response.

Overall, among the 17 responders, there were 8 patients who had a response based on stable platelet counts with transfusion independence for a minimum of 8 consecutive weeks. There were 3 patients who had a response in platelet counts, i.e., they had a platelet count increase > 20,000/μL above baseline. There were 3 patients who had a response based on a reduction in ≥ 4 units of RBC transfusions for 8 consecutive weeks. There were 8 patients who had a response in the absolute neutrophil count. The table below shows the response criteria which qualified patients as responders for the 17 responders in the study.

Table 5. Response Criteria Totals

Patient #	Age (Years)	Sex	Plt Resp	Plt Tx Resp	Hgb Resp	RBC Tx Resp	ANC Resp
(b) (6)	46	M		Y			Y
	19	M		Y			
	25	M		Y			
	28	M	Y				Y
	45	M		Y			
	41	M		Y			
	77	F					Y
	28	F		Y			
	74	F					Y
	51	M		Y			Y
	66	M		Y			
	66	M	Y				
	66	F					Y
	30	F				Y	
	63	M	Y			Y	Y
	67	M				Y	
	37	F					Y
Response Total			3	8	0	3	8

Plt Resp = Platelet response; Plt Tx Resp = Platelet transfusion response; Hgb Resp = Hemoglobin response; RBC Tx Resp = Red Blood Cell (RBC) transfusion response; ANC Resp = Absolute neutrophil count response; F = Female; M = Male; Y = Response for that criterion; Blank = No response for that criterion
Reviewer table derived from sponsor table ADEFFxpt

Duration of response was defined as the number of months from the date of first response until the date of a relapse or last response assessment as of the data cut-off date. According to the sponsor's duration of response analysis only patients with at least 2 response assessments are included in the duration of response assessment. There were 17/43 patients who met one of the response criteria. There were 5 patients who did not have at least 2 response assessments and were not evaluable for response duration analysis (2 patients did not have a month 3 extension follow-up and 3 patients had not reached the 3 month extension visit by the time of the data cut off. Therefore, the median duration of response for the remaining 12 patients was 14.8 months (range 3-42 months). The median duration of platelet transfusion independence was 200 days (range 9-1096 days). The median duration of RBC transfusion independence was 208 days (range 15-1082 days).

The majority of responders i.e., 14/17, 82% maintained their response as of the data cut-off. There were 3 patients who did not maintain a response at the 3 month

extension time point of the study. Patient (b) (6) had a baseline ANC of 170/μL which improved to 470/μL after 3 months of eltrombopag therapy but then relapsed by the time of the 3 month extension visit (ANC = 290/μL). Eltrombopag was discontinued and the patient subsequently died due to sepsis. Patient (b) (6) discontinued eltrombopag after 3 months of therapy after having lost red blood cell transfusion independence. Eltrombopag was subsequently discontinued and the patients were treated with supportive care.

The sponsor reported that Patients (b) (6) met protocol specified tri-lineage hematopoiesis criteria for at least 8 weeks and were tapered off eltrombopag
All four subjects have maintained tri-lineage hematopoiesis since discontinuing eltrombopag treatment (median follow-up 8.1 months; range 7.2 – 10.6 months) and all remain in response as of the clinical cut-off date, i.e., June 1, 2013.

6.1.7 Subpopulations

In this trial there were 2 patients enrolled who were age 17 years (Patient (b) (6)). No patients younger than age 17 years were enrolled.

- Patient (b) (6) was a black male age 17 years who required red blood cell and platelet transfusions for support of his SAA. The patient was previously treated for the SAA with horse and rabbit ATG as well as cyclosporine, tacrolimus and mycophenolate mofetil. The patient was treated with eltrombopag per protocol. The maximum dose of eltrombopag was 150mg orally once daily by month 3 of therapy at which point eltrombopag was discontinued due to no response. Bone marrow assessment prior to therapy showed markedly hypocellular marrow with tri-lineage hypoplasia. A bone marrow performed at the end of therapy continued to show similar results. No marrow fibrosis or reticulin formation was noted. Cytogenetics were abnormal before and after therapy, i.e., 46 XY +1, DER 91;70 (q10;p10)[4]/46, XY [16] prior to therapy and 45 XY, -7[2]/46, XY [18] after therapy. The patient had one serious adverse event (SAE) of neutropenic fever. Other adverse events (AEs) were mild and consisted of itching, cough, diarrhea, gingival bleeding and rash. The patient was diagnosed with MDS and referred to transplant.

- Patient (b) (6) was a Hispanic male age 17 years who required red blood cell and platelet transfusions for support of his SAA. The patient was previously treated for SAA with horse ATG, corticosteroids, cyclosporine and cyclophosphamide
He was treated with eltrombopag per protocol. The maximum dose of eltrombopag was 150mg orally once daily. Bone marrow biopsy results before and after therapy were similar which showed markedly hypocellular bone marrow and tri-lineage hypoplasia. Eltrombopag therapy was discontinued after 3 months of therapy due to no response. No abnormal cytogenetics were noted.

The patient had no serious adverse events. Mild adverse events included insomnia, pruritus, nausea and ganglion cyst.

Reviewer comment for section 6:

Current therapies for SAA are generally poorly tolerated, require hospitalization and close patient monitoring often in an intensive care unit setting. Response to current therapy is often limited or poor. For example, in one study, in 43 patients with SAA previously treated with a combination of four doses of rabbit ATG and cyclosporine administered for 6 months there were 22 patients who were refractory to this combination IST and 21 patients who relapsed after this combination IST. In this study SAA was defined as an ANC <500/μL and platelet count < 20,000/μL. Response was defined as no longer satisfying the criteria for SAA at 3 months after ATG. After re-treatment with the same combination of rabbit ATG and cyclosporine the overall response rate was 30% in patients who were refractory to IST and 65% in patients who had relapsed after IST. Notably, in this study, 7 patients developed a clonal hematological disorder. The outcomes of the patients with clonal disorders are discussed in section 7.3.4 Significant Adverse Events in this review. There were 13 patients who died of which 3 were responders, 6 were non-responders and 4 patients died without a response assessment. (Scheinberg 2006)

In the medical literature there is one report of eltrombopag therapy for the treatment of two patients with SAA. (Direncli, 2013) One of the patients was a male age 19 years who had pancytopenia diagnosed after an episode of epistaxis and bruising. Subsequent evaluation of the patient's bone marrow showed tri-lineage hypoplasia and a diagnosis of SAA was confirmed. The patient was treated with corticosteroids, horse ATG and cyclosporine. The patient required transfusion support with platelets and red blood cells. The patient was started on eltrombopag 50mg orally once daily. The authors report that the patient's platelet count was < 50,000/μL despite one week of eltrombopag therapy but he did not require platelet transfusion support. The authors reported no change in Hgb or neutrophil counts. The patient developed a fungal infection of the face with mucormycosis. Subsequently the patient became septic and died. The second reported patient was a 44 year old female who was diagnosed with SAA after an episode of epistaxis and bleeding from the ears and intracranial hemorrhage. Subsequent bone marrow evaluation revealed tri-lineage hypoplasia. The patient required platelet transfusion support. The patient was treated with corticosteroids and cyclosporine. The patient was also treated with eltrombopag 50mg orally once daily. The authors reported that the patient had an elevation in her liver transaminases (levels not reported) which decreased to normal after the dose of eltrombopag was decreased to 25mg orally once daily. The authors reported that the patient did not require subsequent platelet transfusions but platelet counts remained < 100,000/μL. The patient's eltrombopag dose was increased to 50mg orally once daily and liver enzymes remained normal. The authors report that the patient's platelet count

increased to a maximum of 80,000/µL. There were no changes in the patient's Hgb or neutrophil counts. The patient was subsequently referred for bone marrow transplant.

The efficacy of eltrombopag therapy for the treatment of patients with SAA who had an insufficient response to previous IST was demonstrated in trial ELT112523. Nearly all patients (36/43, 83%) had at least 2 prior therapies for their SAA. In the trial ELT112523, there were 17/43 (40%) of patients with SAA who had an insufficient response to prior IST who had a hematologic response after a median 12 weeks (range 8-14 weeks) of therapy with eltrombopag. There were 4/17 responders who had multi-lineage responses. As might be expected, among those patients who responded there were 8 patients who had a platelet response based on stable platelet counts with transfusion independence for a minimum of 8 consecutive weeks. Three patients had a response in platelet counts, i.e., they had a platelet count increase > 20,000/µL above baseline. However, there were 8 patients who had a neutrophil response. There were 3 patients who had a response based on a reduction in ≥ 4 units of RBC transfusions for 8 consecutive weeks. Clinically a reduction in transfusion requirements is important due to the decreased use of these medical resources. An increase in neutrophil count can help prevent infections in these patients. The starting dose of eltrombopag was 50mg orally once daily. The starting dose of eltrombopag was decreased for patients of East Asian ancestry, i.e., 25mg orally once daily, similar to the labeled recommendation for the dosing of eltrombopag in the approved eltrombopag indications, i.e., immune thrombocytopenic purpura (ITP) and chronic hepatitis C virus infection (HCV). In trial ELT112523, 40 patients were dose escalated to the maximum protocol allowed dose of eltrombopag 150mg orally once daily. There were 3 patients who reached a maximum eltrombopag dose of 125mg orally once daily. Although it is difficult to do cross study comparisons, the efficacy results of trial ELT112523 are generally similar to those from published literature. These results demonstrate that eltrombopag can be effective treatment for patients with SAA who have had an insufficient response to therapy.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Study ELT112523 was used to evaluate the safety profile of eltrombopag for the treatment of patients with SAA who had an insufficient response to IST. In this study 43 patients were included in the safety database.

7.1.2 Categorization of Adverse Events

Adverse events were graded according to the National Cancer Institute – Common Terminology for Adverse Events (NCI-CTCAE) v.3.0. Adverse events on-therapy were defined as those that occurred from the date of first dose of eltrombopag treatment, to the date of last dose of eltrombopag treatment and until 30 days following the last dose of eltrombopag.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Only one trial, i.e., trial ELT112523, was submitted by the sponsor to support the safety evaluation of eltrombopag for the proposed indication.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In trial ELT112523, 43 patients initiated treatment with eltrombopag 25mg orally once daily for patients of East Asian Ancestry (n = 1) or 50mg orally once daily for all others (n = 42) and were dose escalated in 25 mg increments every 2 weeks to a maximum of eltrombopag 150mg orally once daily. There were 3 patients who received eltrombopag 125mg orally once daily. The planned treatment was three months. Treatment was extended at the same dose in patients who responded. The median time on treatment was 3.6 months (range 2-37 months). The overall median daily dose of eltrombopag was 110mg orally once daily (range 47mg-146mg once daily).

The table below shows the overall exposure to study drug. There were 33/43 (77%) of patients treated for ≥ 3 months and 7/43 (16%) of patients treated for > 12 months. Patients who did not respond after 3 months of therapy were discontinued from treatment.

Table 6. Overall Exposure to Study Drug

Time on Treatment (months)	**Eltrombopag (n=43) n (%)**
< 3	10 (23)
≥ 3	33 (77)
> 6	11 (26)
> 12	7(16)

Derived from Sponsor's table Module 5.3.5.2 ELT112523 Study Report page 49

The median duration of therapy at the 150mg dose of eltrombopag was 1.4 months (range 0-33 months). The table below shows the total time on treatment for the 40 patients who were escalated to the maximum dose of eltrombopag allowed in this study, i.e., 150mg orally once daily. Most patients were treated at the maximum dose of eltrombopag (150mg) < 3 months.

Table 7. Exposure to Eltrombopag 150mg Orally Once Daily

Time on Treatment (months)	**Eltrombopag (n=40) n (%)**
< 3	27 (63)
≥ 3	5 (12)
> 6	3 (7)
> 12	5(12)

Derived from Sponsor's table Module 5.3.5.2 ELT112523 Study Report page 268

7.2.2 Explorations for Dose Response

In trial ELT112523 nearly all patients 40/43 (93%) were dose escalated to the maximum protocol allowed dose of eltrombopag 150mg orally once daily. Patients (b) (6) (b) (6) received a maximum dose of eltrombopag of 125mg orally once daily.

- Patient (b) (6) had study drug discontinued due to abdominal discomfort on day 59 of therapy. Patient (b) (6) had study drug discontinued due to acute hepatitis B infection on day 61 of therapy.

- Patient (b) (6) required a study drug dose interruption on day 17 due to a SAE of nausea and vomiting which required hospitalization. At that time the patient was being treated with eltrombopag 75mg orally once daily. The dose of study drug was restarted after resolution of the SAE on day 18. However, on day 39 of therapy the patient had elevated transaminases (aspartate aminotransferase (AST) 98U/L and alanine aminotransferase (ALT) 206U/L). At that time the patient was being treated with eltrombopag 100mg orally once daily. Eltrombopag was restarted at a dose of 75mg orally once daily after the liver transaminase levels returned to normal on day 43. On day 74 the patient's liver transaminases again started to increase and eltrombopag therapy was once again interrupted. At that time the patient was being treated with eltrombopag 100mg orally once daily. The patient was restarted and maintained on eltrombopag 75mg orally once daily on day 88 after resolution of the mildly elevated liver transaminases.

7.2.3 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Eltrombopag and romiplostim are thrombopoietin (TPO) receptor agonists. Compared to romiplostim, eltrombopag is an orally administered small molecule TPO receptor

agonist whereas romiplostim is an injectable peptibody. Eltrombopag and romiplostim share certain similar limitations of use, i.e., both drugs should not be used to normalize platelet counts and both drugs should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding. However, there are some differences in the limitations of use between eltrombopag and romiplostim limitations of use as well. The eltrombopag limitations of use that are different compared to the romiplostim limitations of use are as follows:

- Eltrombopag 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.
- The safety and efficacy of eltrombopag have not been established in combination with direct acting antiviral agents approved for treatment of chronic hepatitis C genotype 1 infection.

The limitations of use for romiplostim that are different compared to the eltrombopag limitations of use are as follows:

- Romiplostim is not indicated for the treatment of thrombocytopenia due to myelodysplastic syndrome (MDS) or any cause of thrombocytopenia other than chronic ITP.

This limitation of use for romiplostim was included in the product label because in patients with MDS, romiplostim increases blast cell counts and increases the risk of progression to acute myeloid leukemia (AML). This does not appear to be the case for eltrombopag. Based on clinical reviews completed by Dr. Andrew Dmytrijuk on July 12, 2013 and November 27, 2012 of the eltrombopag Risk Evaluation and Mitigation Strategy (REMS) program, eltrombopag therapy did not appear to increase the risk of hematologic malignancies, i.e., acute leukemia, and progression of malignancy in patients with a pre-existing hematological malignancy or myelodysplastic syndrome (MDS).

Furthermore, early in the development of eltrombopag for the indication in immune thrombocytopenic purpura, there was concern that eltrombopag may increase the risk of myelofibrosis and/or reticulin formation (see clinical review by Dr. Dmytrijuk completed September 12, 2008). A warning regarding this risk was included with subsequent approved product labels. In subsequent clinical reviews of the assessment of the eltrombopag REMS program and post-marketing Periodic Safety Update Reports (PSURs) Dr. Dmytrijuk concluded that there does not appear to be an increased risk for myelofibrosis and that the bone marrow reticulin formation and risk for bone marrow fibrosis could be removed from the label (see clinical review by Dr. Dmytrijuk completed on July 9, 2013). In NDA 22291 supplement 10 supporting document 418 letter date August 16, 2013 the sponsor agreed to the proposed change to the label to remove the

risk for myelofibrosis and that the bone marrow reticulin formation and risk for bone marrow fibrosis (see clinical review by Dr. Dmytrijuk completed September 23, 2013).

Liver transaminase elevation is a known adverse reaction with eltrombopag. The eltrombopag product label states that the drug should be discontinued if alanine aminotransferase (ALT) levels increase to ≥ 3X ULN in patients with normal baseline liver function or ≥ to 3X baseline in patients with pre-treatment elevations in transaminases.

Another adverse reaction that can occur with TPO receptor agonists is thrombosis. This adverse event related to eltrombopag treatment of patients with HCV is reviewed in section 7.3.4 of this review below.

7.3 Major Safety Results

7.3.1 Deaths

In ELT112523 six patients died during the study. No patients died while still on eltrombopag therapy. There were 2 patients who died ≤ 30 days after the last dose of study medication. Patient (b) (6) died on day 100 of the study, 8 days after treatment discontinuation due to septic shock and patient (b) (6) died on day 248 of the study, 22 days after treatment discontinuation due to septic shock. In both cases the deaths were considered to be related to SAA.

- Patient (b) (6) was a female African-American age 25 years with SAA for which she was previously treated with rabbit and horse ATG, cyclosporine and androgen therapy. The patient required platelet and red blood cell transfusion support. The past medical history consisted of *klebsiella* bacteremia, epistaxis, urinary tract infection, viral gastroenteritis and peri-rectal abscess. The patient's baseline bone marrow report showed tri-lineage hypoplasia and cytogenetic analysis was normal. The patient was treated with up to 150mg of eltrombopag once daily for 12 weeks. The patient was discontinued from study medication due to no response. Follow-up bone marrow biopsy and cytogenetic assessment was not performed. On day 96 the patient developed febrile neutropenia which required intensive care unit admission and monitoring. Blood cultures were positive for gram negative rods and liver abscess. The patient was treated with levofloxacin. The patient became progressively more hypotensive and died due to septic shock on day 100.

- Patient (b) (6) was a white female age 77 years with SAA. Previously the SAA was treated with horse ATG, tacrolimus, cyclosporine and corticosteroids. The patient required red blood cell and platelet transfusion support. The patient's past medical history was significant for bacterial pneumonia, hypertension, renal

failure, hemosiderosis, urinary tract infections, leg cellulitis and bruising. The baseline bone marrow showed tri-lineage hypoplasia with some evidence of left shift and dysplastic changes. Cytogenetic assessment at baseline was normal. The patient was treated with up to 150mg of eltrombopag orally once daily through day 226 due to response to eltrombopag therapy. Follow-up cytogenetic analysis on week 16 was normal. The bone marrow biopsy showed hypocellular marrow with progressive myeloid and erythroid maturation with increased blasts. On day 227 the patient presented with fever and disorientation, fatigue and myalgia. The patient was treated with intravenous antibiotics, intravenous fluids and filgrastim. Blood cultures were negative and the patient was admitted to hospital with a diagnosis of viral infection. On day 235 the fever resolved but the patient was weak and bedridden. The patient decided to discontinue therapy and she was transferred to hospice care. The patient died on day 248 with presumptive diagnosis of viral infection.

There were 4 patients who died > 30 days after treatment discontinuation. Patient (b) (6) died 195 days after treatment discontinuation, Patient (b) (6) died 122 days after treatment discontinuation, patient (b) (6) died 163 days after treatment discontinuation and patient (b) (6) died 116 days after treatment discontinuation. The deaths of patients (b) (6) were considered to be related to SAA and these patients died due to sepsis. Patient (b) (6) cause of death was unknown.

- Patient (b) (6) was a white male age 59 years with SAA diagnosed 2 years prior to study entry. Prior therapy for his SAA included horse ATG, alemtuzumab and androgen therapy. Past medical history include benign prostatic hypertrophy, chronic low back pain and iron overload for which he was treated with off label deferasirox. The patient required platelet and red blood cell transfusion support. His baseline Bone marrow biopsy at baseline showed fibrosis, 'dyspoietic maturation' but was otherwise consistent with SAA with showed tri-lineage hypoplasia. The patient was treated with eltrombopag up to 150mg orally once daily for 12 weeks but was discontinued from therapy due to no response. On Day 84 cytogenetic analysis showed 45, XY,-7[4]/46,XY[16], in 4/20 metaphases and was detected again in 20/20 metaphases and a bone marrow biopsy showed dysplasia at a second follow-up on day 133. A diagnosis of MDS was made based upon the cytogenetic abnormality and the dysplasia noted in the bone marrow and the patient was referred for bone marrow transplant. However, the patient died on day 195.

7.3.2 Nonfatal Serious Adverse Events

The table below shows the serious adverse events (SAEs) that occurred in ≥ 2 patients in ELT112523. The most common SAEs included febrile neutropenia, sepsis and viral infections.

Table 8. Serious Adverse Events in ≥ 2 Patients

Adverse Event	**Eltrombopag (n=43) n (%)**
Febrile Neutropenia	6 (14)
Sepsis	2 (5)
Viral Infection	2 (5)

Derived from Sponsor's table Module 5.3.5.2 ELT112523 Study Report page 55

7.3.3 Dropouts and/or Discontinuations

There were 4 patients who had adverse events leading to premature discontinuation from the study. Patients (b) (6) were discontinued from the study prematurely. The adverse reactions leading to discontinuation included cataract formation, abdominal pain, acute hepatitis B and sepsis, respectively.

7.3.4 Significant Adverse Events

Overall there were 9 patients who had elevated liver transaminases > 3x upper limit of normal (ULN) and there were 0 patients with total bilirubin > 2 x ULN. In study ELT112523 there were 2 patients who had elevated ALT > 3xULN and bilirubin > 1.5xULN. In these two cases the indirect bilirubin was primarily elevated and both events were transient. The cases are as follows:

- Patient (b) (6) was a white male age 45 years with SAA and transaminitis secondary to chelation therapy (type of therapy unspecified). The patient was previously treated with rabbit hose ATG, corticosteroids, androgen therapy and cyclosporine beginning in 2009. The patient had a history of transaminitis and had Grade 1 elevations in ALT and alkaline phosphatase (AlkP) and normal aspartate aminotransferase (AST) and bilirubin prior to study entry. The patient received eltrombopag 50 to 150 mg/day from Day 1 through Day 649. Eltrombopag was tapered beginning Day 418 due to continuing efficacy. Transaminase values and total bilirubin peaked at Grade 2 levels on Day 89 (AST 136 IU/L (normal range 9-34 IU/L), ALT 175 IU/L (normal range 6-41 IU/L), bilirubin 29.07µmol/L (normal range 1.71-17.1 µmol/L); direct bilirubin 3.42 µmol/L (normal range 0-3.42 µmol/L). The eltrombopag dose was 150 mg/day at that time. The serum transaminase and bilirubin levels decreased to normal ranges while continuing on eltrombopag 150 mg/day. The patient remained on eltrombopag therapy for an additional 6 months with no further increase in transaminases or bilirubin.

- Patient (b) (6) was an African-American female age 74 years with SAA, diabetes and chronic renal disease. The patient was previously treated with horse and rabbit ATG, alemtuzumab, sirolimus, methotrexate and nandrolone therapy for the SAA beginning in 2004. The patient received eltrombopag 50 to 150 mg/day

from Day 1through Day 111. Study treatment was discontinued on Day 112 and the subject withdrawn from the study on Day 134 due to a serious adverse event (SAE) of sepsis. ALT, AST and bilirubin were normal at baseline and increased during the study. The maximum AST/ALT and bilirubin were Grade 2 which peaked on Day 85 at the Week 12 response assessment (AST 142 IU/L, ALT 178 IU/L, bilirubin 27.36 µmol/L, direct bilirubin 6.84 µmol/L). The normal ranges are the same as for patient (b) (6). There were no changes to study treatment as a result of the transaminase elevations.

There were no thromboembolic events reported during the study.

There were 3 (7%) patients (Patient (b) (6)) who had a cytogenetic abnormality present at baseline. Of the 3 subjects with abnormal karyotype at baseline, 2 subjects had no change in their karyotype during treatment with eltrombopag (duration of treatment 37 and 3 months, respectively) and one subject had an abnormal karyotype at baseline and normal karyotype on subsequent bone marrow examinations during 22 months of treatment with eltrombopag.

There were 7/40 patients with normal karyotype (n = 6) or insufficient samples (n = 1) at baseline who had subsequent cytogenetic abnormalities detected after treatment with eltrombopag. The median time from diagnosis of SAA to the detection of the cytogenetic abnormality was 68 months, i.e., > 5 years (range 18-124 months). The median time from the start of eltrombopag therapy to the detection of the cytogenetic abnormality was 3 months (range 3-14 months). The sponsor's table below shows the cytogenetic abnormalities detected, duration of eltrombopag therapy at the time of the abnormal cytogenetic assessment and clinical outcomes of these patients. The table below shows 5/7 patients had complex cytogenetic abnormalities affecting chromosome 7. All 5 of these patients were non-responders. Patient (b) (6) had an insufficient bone marrow sample at baseline to determine if there was a change in the cytogenetics after therapy with eltrombopag.

Table 9. Summary of Cytogenetic Abnormalities after Eltrombopag Therapy

Subject ID	Cytogenetic abnormality	Treatment Duration (Months)	Dysplasia	Outcome
(b) (6)	45XY,-7[4]/46XY[16]	3	Baseline: 'dyspoietic maturation' Day 133:'findings are worrisome for hypocellular MDS.'	Died of MDS
	+8[9]/46XX[11] +8[2]/46XX[18]	3 1M post-treatment	No	Referred to transplant
	-7[5]/DER(16)t(1:16)[3]/46/XY[12] DER(16)t(1:16)[4]/46XY[16]	3 1M post-treatment	No	Referred to transplant
	DEL(13)[19]/46XY[1]	13.7	Baseline: 'without clear cut dysplasia' Day 419: 'erythroid dominance, L-shift in erythroid maturation with mild megaloblastic changes & occasional (<5%) ringed sideroblast, progressive but mildly L-shift myeloid maturation, mildly decrease megakaryocytes & without increased blast.'	MDS Received a Transplant
	+21[3]/46XY[17] DEL-7[2]/46XY[19]	3 6M post-treatment	Baseline: 'Erythroid predominance & no increase in blasts' Day 274: 'Markedly decreased megakaryocytes erythroid predominance with mild dyserythropoiesis. Less than 5% blasts'	Referred to transplant
	-7[5]46XY[15]	3	No	Referred to transplant
	+1DER(1:7)[4]/46XY[16] (-7[2]/46XY[18])	3 1M post-treatment	No	MDS[c] Received a Transplant

Data Source: Listings 23.0010, 30.0070, 30.0080, 30.0090
a. Non-responder
b. Responder
Sponsor's table Module 5.3.5.2 ELT112523 Study Report page 62

- Patient (b) (6) was discussed previously in section 7.3.1 Deaths in this review.
- Patient (b) (6) was a white male age 66 years with SAA who required red blood cell and platelet transfusions. He was previously treated with horse and rabbit ATG, cyclosporine and tacrolimus. Bone marrow assessment at baseline showed tri-linage hypoplasia without clear evidence of dysplasia. He had a normal cytogenetic analysis at baseline. The patient was treated with eltrombopag up to 150mg orally once daily for 13.7 months. He had a normal karyotype on day 293. Response to eltrombopag was maintained at the last response assessment (Day 384) due to hemoglobin and platelet transfusion response. On Day 419, deletion of chromosome 13 was observed in 19 of 20 metaphases. The bone marrow corresponding to deletion 13 described 'mild megaloblastic changes and occasional (<5% ringed sideroblast)'. A diagnosis of MDS was made based upon both the cytogenetic abnormality and the dysplasia noted in the bone marrow. The subject received a transplant. No SAEs were reported for this patient.
- Patient (b) (6) was discussed previously in section 6.1.7 Subpopulations in this review.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The table below shows the common adverse reactions that occurred in ≥15% of patients in ELT112523. There were no thrombotic adverse events.

Table 10. Adverse Events in ≥ 15% of Patients

Adverse Event	**Eltrombopag n = 43 n (%)**
Nausea	14 (33)
Fatigue	12 (28)
Cough	10 (23)
Diarrhea	9 (21)
Headache	9 (21)
Pain in Extremity	8 (19)

Reviewer table derived from sponsor table AE.xpt

7.4.2 Laboratory Findings

The table below summarizes the proportion of patients with grade 3 or 4 adverse reactions of key clinical laboratory tests while on therapy with eltrombopag. NCI-CTCAE v.3 grades were used to characterize the adverse reactions. The table below shows that there were no grade 4 adverse events of serum chemistries and very few (n = 6) grade 3 liver enzyme adverse events. Hematologic adverse reactions were primarily due to non-response to eltrombopag therapy.

Table 11. Key Laboratory Adverse Events Grade 3 or 4 in ELT112523*

Adverse Event	**Grade 3, n (%)**	**Grade 4, n (%)**
ALT	4(10)	0(0)
AST	2 (2)	0(0)
Total Bilirubin	0(0)	0(0)
Alkaline Phosphatase	0 (0)	0(0)
Albumin	0 (0)	0(0)
Serum Creatinine	0(0)	0(0)
Hemoglobin	15 (36)	7 (17)
Leukocyte	4 (10)	4(10)
Lymphocyte	3 (7)	0(0)
Neutrophils	6 (14)	6 (14)
Platelets	1 (2)	14 (33)

*N=43. ALT = Alanine aminotransferase, AST = Aspartate aminotransferase.
Derived from Sponsor's table Module 5.3.5.2 ELT112523 Study Report pages 358-373

7.4.3 Vital Signs

There were no consistent patterns of change in vital signs in study ELT112513.

7.4.4 Electrocardiograms (ECGs)

Electrocardiography was not routinely performed in this study (see Table 3. Study Schedule in section 5.3 Discussion of Individual Studies in this review).

7.4.6 Immunogenicity

Eltrombopag is a small molecule and is not expected to cause immunogenic reactions. Review of safety data for study ELT112523 did not reveal immunogenicity issues or adverse events.

7.5 Additional Safety Evaluations

7.5.1 Pediatrics

Although children age ≥ 12 were eligible for study enrollment only 2 patients age 17 years were enrolled. The clinical course for these two patients is described in section 6.1.7 Subpopulations in this review.

7.5.2 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No abuse potential is expected with this drug. There are no known antidotes. See the review (completed September 12, 2008) by Dr. Andrew Dmytrijuk of the original NDA 22-291 submission for a discussion of a case of overdose of eltrombopag in the initial clinical development program.

7.6 Additional Submissions

In NDA 22291 supporting document 497 letter date June 19, 2014 the sponsor submitted the 120-Day Safety Update for this current application. In this report the sponsor states 4/43 (9%) of the patients remained on study drug at the time of data cut off for study ELT112523, i.e., June 1, 2013. No new safety issues were identified since the time of submission for the administration of eltrombopag in patients with SAA following review of safety data collected through March 31, 2014.

In this report the sponsor states that based on (b) (4) Health data, it is estimated that approximately (b) (4) patient years of eltrombopag

treatment have been prescribed worldwide as of December 2013. Worldwide no new safety concerns for eltrombopag were reported in the 120-Day Safety Update report

Reviewer comment for section 7: In ELT112523 the most common adverse events (AEs) occurring in ≥20% of patients were nausea, fatigue, cough, diarrhea and headache. The most common serious adverse events (SAEs) occurring in ≥ 5% patients were febrile neutropenia, sepsis and viral infection. There were 6 deaths reported during the study. There were no subjects who died while receiving eltrombopag therapy. There were 2 patients who died within 30 days of the last dose of eltrombopag (both deaths related to sepsis) and 4 patients died > 100 days after the last dose of eltrombopag (2 deaths due to sepsis, 1 AML (patient (b) (6) and 1 cause of death was unknown but occurred 116 days from the last dose of eltrombopag). There were 7/43 patients who had new cytogenetic abnormalities reported, including 5 patients who had complex changes in chromosome 7. Patient (b) (6) was on eltrombopag therapy for a period of 3 months and was noted to have abnormal hematopoietic maturation at baseline. There were 3 patients with baseline cytogenetic abnormalities. There were no thromboembolic AEs reported. Hepatobiliary AEs grade 3 or 4 elevations in serum liver transaminases or elevated serum bilirubin levels were reported in 6/43 patients according to NCI-CTCAE v.3.0 Criteria. In two patients (Patients (b) (6)) had alanine aminotransferase (ALT) elevation > 3 x upper limit of normal (ULN) and total bilirubin > 1.5 x ULN (see section 7.3.4 for a detailed discussion of these 2 cases). However, in both cases the indirect bilirubin was elevated. There were 4 patients in which AEs lead to premature discontinuation of eltrombopag therapy (including cataract, abdominal discomfort, hepatitis B infection and sepsis). There were no thromboembolic adverse reactions reported. There were 2 patients age <18 years enrolled in the study. Both patients were non-responders. In general, therapy with eltrombopag in patients with SAA resulted in similar frequencies and types of adverse reactions.

8 Postmarket Experience

In the current efficacy supplement the sponsor states that the worldwide exposure to eltrombopag is (b) (4) patient years as of June 2013.

At the time of approval in the United States in 2008, a Risk Evaluation and Mitigation Strategy (REMS) program was implemented for eltrombopag, called PROMACTA Cares. The REMS was a restricted distribution program that consisted of a patient registry of all patients who receive eltrombopag in the United States. The goal of the REMS included the assessment of the overall long-term safety and safe use of eltrombopag through periodic monitoring. On December 6, 2011 a Supplemental Approval Remove REMS Elements REMS Modification letter was sent to the sponsor which approved changes to REMS requirements for eltrombopag. The main modifications included the removal of the restricted distribution and the removal of additional collection of safety data through the United States REMS program. In NDA 22-291 supporting document 473 letter date April 23, 2014 the sponsor requested an

elimination of the Risks Evaluation and Mitigation Strategy (REMS) for eltrombopag. The clinical review by Dr. Andrew Dmytrijuk, from the Division of Hematology Products (final signature date April 28, 2014) states that the sponsor's request is reasonable because the REMS program has substantiated the overall safety of eltrombopag as concluded in his previous reviews final signature dates November 27, 2012 and July 12, 2013, of the REMS Assessment submitted in NDA 22-291 supporting document 313 letter date June 29, 2013 and the Periodic Safety Update Report (PSUR) submitted in NDA 22-291 supporting document 349 letter date January 18, 2013. Dr. Dmytrijuk's review recommended that the sponsor's request to eliminate the REMS for eltrombopag be granted. A review by Dr. Suzanne Robottom, Division of Risk Management (final signature date July 1, 2014) states that the REMS program for eltrombopag is no longer necessary to ensure that the benefits of eltrombopag outweigh the risks. The review by Dr. Robottom concurs with the DHP recommendation to eliminate the eltrombopag REMS program.

9 Appendices

9.1 Literature Review/References

Ades, L. et al.: Long-term outcome after bone marrow transplantation for severe aplastic anemia. 2004. Blood. 103(7):2490-2497.

Biswajit. H. et al.: Aplastic anemia. 2012. N. Am. J. Med. Sci. 4(9):384-388.

Chawla, S.P. et al.: Results of a phase 1 dose escalation study of eltrombopag in patients with advanced soft tissue sarcoma receiving doxorubicin and ifosfamide. 2013. BMC Cancer. 13:121-130.

Desmond, R. et al.: Eltrombopag restores tri-lineage hematopoiesis in refractory severe aplastic anemia that can be sustained on discontinuation of drug. 2014. Blood. 123(12):1818-1825.

Direncli, C. et al.: The impact of eltrombopag administration on the clinical course of severe refractory fatal acquired aplastic anemia. 2013. Turk. J. Hematol. 30:328-330.

Gupta, V. et al.: Clinical relevance of cytogenetic abnormalities at diagnosis of acquired aplastic anemia in adults. 2006. Br. J. Hematology, 134(1):95-99.

Lee, J.H. et al.: Spontaneous remission of aplastic anemia. 2001. Hematologica. 86:928-933.

Lichtman, M.A. et al.: Williams Manual of Hematology 6th ed. 2003.

Mikhailova, N. et al.: Cytogenetic abnormalities in patients with severe aplastic anemia. 1996. Hematologica. 81:418-422.

Rosenfeld, S. et al.: Antithymocyte globulin and cyclosporine for severe aplastic anemia. 2003. JAMA. 289(9): 1130-1135.

Scheinberg, P. et al.: Retreatment with rabbit antithymocyte globulin and cyclosporine for patients with relapsed or refractory severe aplastic anemia. 2006. Br. J. Hematol. 133(6):622-628.

Sun, H. et al.: Eltrombopag a thrombopoietin receptor agonist enhances human umbilical cord blood hematopoietic stem/primitive progenitor cell expansion and promotes multi-lineage hematopoiesis. 2012. Stem Cell Res. 9(2):77-86.

9.2 Advisory Committee Meeting

Not applicable – no Advisory Committee Meeting was held for this supplement.

9.3 Labeling Recommendations

The proposed draft label incorporating my recommendations for changes is shown below. Proposed additions are underlined and deletions are in strike-through notation. Final wording of the labeling is being negotiated with the sponsor.

The key proposed labeling changes include:

- The proposed indication should state that eltrombopag is indicated for the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy. This wording should be used in the Highlights section, Indications and Usage section § 1.3 subheading and in other sections of the label which refer to this indication.
- In section 2 Dosage and Administration § 2.3 the dosing of eltrombopag should be clarified for patients who achieve tri-lineage response including transfusion independence lasting at least 8 weeks. For these patients the dose of eltrombopag should be reduced by 50%.
- In section 6.1 Clinical Trial Experience the word “complex” should be added to describe the cytogenetic changes that were observed in 5 patients who had changes in chromosome 7.
- In section 14 Clinical Studies § 14.3 the wording regarding bi-lineage or tri-lineage responses should be clarified to state that these responses were observed in 4/43 (9%) of patients.

28 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ANDREW DMYTRIJUK
08/15/2014

KATHY M ROBIE SUH
08/18/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22291Orig1s012

PRODUCT QUALITY REVIEW(S)

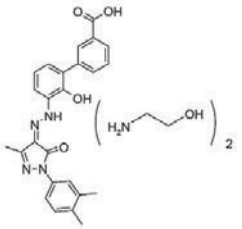
CHEMIST'S REVIEW	1. ORGANIZATION	2. NDA NUMBER
	OHOP, DHP	22291, S-012
3. NAME AND ADDRESS OF APPLICANT		4. COMMUNICATION, DATE
GlaxoSmithKline LLC Corporate Service Company 2711 Centerville Road, Suite 400 Wilmington, DE 19808		27-Feb-2014
5. PROPRIETARY NAME	6. NAME OF THE DRUG	
Promacta Tablets	Eltrombopag olamine	
8. SUPPLEMENT PROVIDES FOR:		
A new indication: PROMACTA is indicated for the treatment of cytopenias in patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy		
9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
selective STAT activator	Rx	
12. DOSAGE FORM	13. POTENCY	
Tablets	12.5 mg, 25 mg, 50mg, 75 mg, 100 mg	
14. CHEMICAL NAME AND STRUCTURE		

Chemical Name: 3'-{(2Z)-2-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene]hydrazino}-2'-hydroxy-3-biphenylcarboxylic acid - 2-aminoethanol (1:2).

Molecular Formula: $C_{25}H_{22}N_4O_4 \cdot 2(C_2H_7NO)$

Molecular Weight: 564.65 eltrombopag olamine and 442.5 for eltrombopag free acid

CAS Number: [*496775-62-3*]



15. COMMENTS
The applicant has requested a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR, part 25, §25.31(b) for eltrombopag olamine. This supplement meets the requirements of a categorical exclusion under 21 CFR §25.31(b) since the concentration of the active moiety at the point of entry into the aquatic environment will be less than 1 ppb. To the best of Novartis's knowledge, no extraordinary circumstances exist in regards to these actions. The applicant's request for a categorical exclusion is accepted. The CMC editorial changes in the proposed label are also acceptable.
16. CONCLUSION AND RECOMMENDATION
The supplement is recommended for approval from a CMC standpoint.

17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
JANICE BROWN	See electronic signature stamp	18-Jul-2014
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/s/

JANICE T BROWN
07/18/2014

HASMUKH B PATEL
07/18/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22291Orig1s012

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	022291
Supplement #:	12
Drug Name:	Promacta® (eltrombopag) Tablets
Indication:	The treatment of cytopenias in patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy
Applicant:	GlaxoSmithKline
Received Date:	February 27, 2014
PDUFA Date:	August 27, 2014
Review Type:	Priority
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Xiaoping (Janet) Jiang, PhD
Concurring Reviewers:	Yuan-Li Shen, Dr. PH, Team Leader
	Rajeshwari Sridhara, PhD, Division Director
Medical Division:	Division of Hematology Products
Clinical Team:	Andrew Dmytrijuk, MD, Clinical Reviewer
	Kathy M. Robie Suh, MD, Clinical Team Leader
	Ann T. Farrell, MD, Division Director
Project Manager:	Tinya Sensie

Keywords: point estimates, 95% Clopper-Pearson confidence intervals

Table of Contents

1 EXECUTIVE SUMMARY

On February 27, 2014, the applicant submitted a supplemental new drug application (sNDA) to seek an approval of Promacta® (eltrombopag) tablets for the proposed indication '*the treatment of cytopenias in patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy'*. The submission included the data and results from the pivotal study NIH 09-H-0154/ELT112523 entitled 'A Pilot Study of a Thrombopoietin-receptor Agonist (TPO-R agonist), Eltrombopag, in Aplastic Anemia Patients with Immunosuppressive-therapy Refractory Thrombocytopenia', and an ongoing study NIH 12-H- 0150/ELT116643.

A total of 44 patients with severe aplastic anemia (SAA) were enrolled in Study ELT112523. Among the 44 patients, 43 patients received at least one dose of eltrombopag. The primary endpoint was the proportion of responders who had changes in the platelet count and/or platelet transfusion requirements, hemoglobin levels, number of red blood cell transfusions, or neutrophil counts as measured by International Working Group criteria and the toxicity profile as measured using the CTCAE criteria. The primary analysis was to provide descriptive statistics such as point estimates and 95% Clopper-Pearson confidence interval. Based on the data from 44 enrolled patients in Study ELT112523, the estimated percentage of responders was 38.5% [95% confidence interval (CI): 24.2%, 53.0%]. The median duration of response was not reached by the time of data cut-off for the final analysis. There were 14 responders who maintained their response at the date of the data cut-off for the Clinical Study Report (CSR). No statistical comparison was conducted in the study and therefore no statistical inference can be drawn from the study.

It is noted that Study ELT112523 was conducted in a single center, thus the reproducibility and subsequent generalization of the results from Study ELT112523 may be problematic. However, given that SAA is a rare disease and the application is for a supplemental indication, the adequacy of the study to support an approval and whether the results from Study ELT112523 provide a favorable benefit to risk ratio to support an approval of Eltrombopag for the proposed indication will be determined by the clinical review team.

2 INTRODUCTION

2.1 Overview

Promacta® (eltrombopag) has been approved for the following indications: 1) thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenia (ITP) who has had an insufficient response to corticosteroids, immunoglobulins, or splenectomy; 2) thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. In this sNDA, the applicant submitted the data from the pivotal study ELT112523 and other studies to seek an approval of eltrombopag for a proposed indication of the treatment of cytopenias in patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy. The annual incidence of aplastic anemia is about 2 cases per million population with a higher incidence in East Asian countries (about 4-7 cases per million).

The pivotal study ELT112523 was single-arm, single-center, and open-label. The primary objective of the study was to assess the safety and efficacy of the oral thrombopoietin receptor

agonist (TPOR agonist) eltrombopag in aplastic anemia patients with immunosuppressive-therapy refractory thrombocytopenia. ELT112523 was conducted at one center (NIH) in one country (US). ELT112523 was initiated on June 23, 2009 and the data cut-off date was June 1, 2013. The secondary objectives of the study included the analyses of the incidence and severity of bleeding episodes, and the impact on quality of life.

2.2 Data Sources

Data used for this review were from the electronic submission received on February 27, 2014. The link was "\\CDSESUB1\EVSPROD\NDA022291\022291.enx"

3 STATISTICAL EVALUATION

This section mainly focuses on efficacy evaluation for the pivotal study ELT112523.

3.1 Data and Analysis Quality

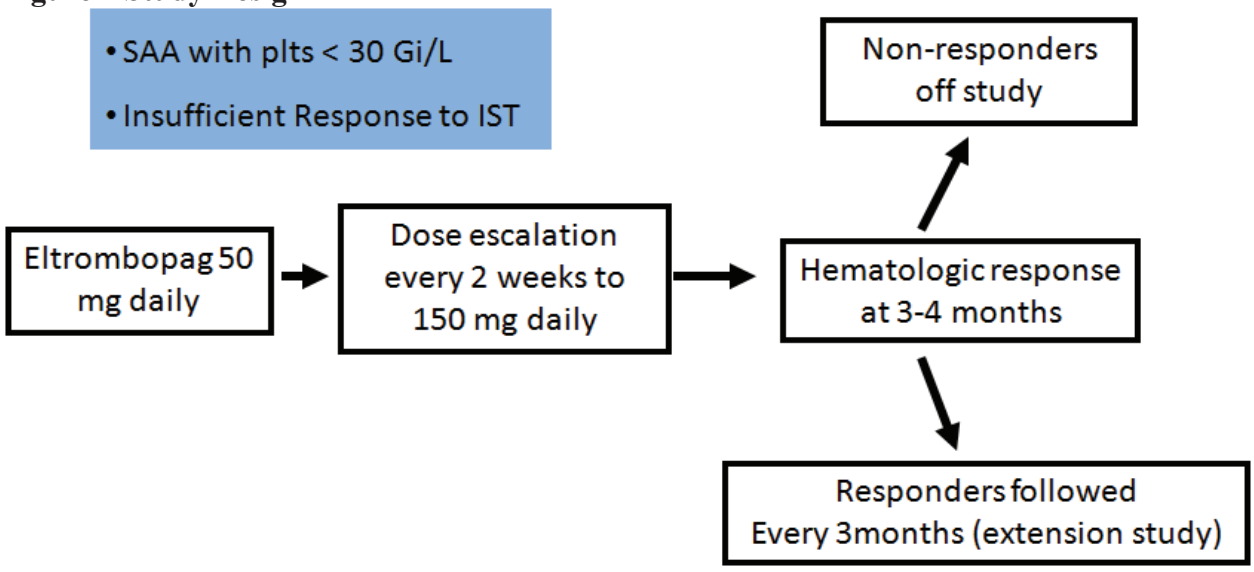
The quality of submitted data allowed this reviewer to replicate the applicant's primary analysis and other submitted efficacy results and conduct the reviewer's own analyses. The report and analysis plan (RAP) was provided in the sNDA submission.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

ELT112523 was a non-randomized, dose modification study. The inclusion criterion of the study included diagnosis of aplastic anemia**,** with refractory thrombocytopenia following at least one treatment course of horse or rabbit ATG/cyclosporine; platelet count ≤ 30,000/μL; and age ≥ 12 years old. Figure 1 shows the overall study design of Study ELT112523.

Figure 1 Study Design



Per the protocol, the primary endpoint was the proportion of drug responders who had changes in the platelet count and/or platelet transfusion requirements, hemoglobin levels, number of red

blood cell transfusions, or neutrophil counts as measured by International Working Group criteria and the toxicity profile as measured using the CTCAE criteria. The platelet response, erythroid response, and neutrophil response were defined as follows:

- Platelet response: platelet count increases to 20,000/μL above baseline at three months, or stable platelet counts with transfusion independence for a minimum of 8 weeks

- Erythroid response: an increase in hemoglobin by ≥1.5 g/dL in patients with a pre-treatment hemoglobin <9 g/dL without packed red blood cell (PRBC) transfusion support, or an absolute reduction of at least 4 red blood cell (RBC) transfusions for 8 consecutive weeks, compared to the number of transfusions in the 8 weeks pretreatment

- Neutrophil response: at least 100% increase in absolute neutrophil count (ANC) in patients with a pre-treatment ANC of $< 0.5 \times 10^9$/L, or an ANC increase $>0.5 \times 10^9$/L

The primary endpoint was measured at 12 weeks, or 16 weeks for patients with sufficient activity who were eligible to continue study medication for an additional 4 weeks to ensure response criteria were met to enter the extended access portion of the trial.

The secondary endpoints in the study included change in platelet count (continuous variable), incidence of bleeding, change in serum thrombopoietin level (as measured by enzyme-linked immunosorbent assay, (b) (4), and health related quality of life (as measured by the Medical Outcomes Study 36-Item Short Form General Health Survey, version 2 [SF36v2]; Quality-Metric) measured at 12 weeks.

Reviewer's Comments:

1. *The endpoint of duration of response was not specified in the protocol and its amendments. However, in the submitted reporting analysis plan (RAP), duration of response was defined for the patients who responded at the Week 12-16 visit as the number of months from the first date of a response until the first date of a relapse or the date the patient was last assessed.*

3.2.2 Statistical Methodologies

There was no formal test of hypothesis planned for ELT112523. The study was originally designed as a two-stage trial with a maximum of 25 patients to test the null hypothesis that the response rate with this treatment was no greater than 10%. The sample size of 25 patients was determined by testing the null hypothesis H_0: $p \leq 10\%$ versus the alternative H_1: $p \geq 30\%$ at a significance level of 0.05 and a power of 80%. At the first stage, 15 patients were accrued and the null hypothesis would not be rejected if no more than 1 patient responds to the treatment within 12 weeks. If 2 or more patients responded to the treatment within 12 weeks at the first stage, then an additional 10 patients would be accrued, bringing the total number of patients to 25. The null hypothesis of $p \leq 10\%$ would be accepted if the total number of responders within 12 weeks was 5 or less. The protocol Amendments L (April 20, 2012) and Q (Feb 05, 2013) increased the sample size from 25 to 45 and then from 45 to 50 respectively, provided the

justification that adding 25 patients would narrow the confidence intervals and get more safety data.

The primary analysis was to use point estimates and 95% Clopper-Pearson confidence interval to summarize the response rate. Because a responder could be a patient who had response according to one or more of three criteria: platelets (platelet counts and/or platelet transfusions), red cells (hemoglobin level and/or RBC transfusions), and neutrophils (ANC counts). There were 7 possible response combinations:

1) Platelets
2) Red Cells
3) Neutrophils
4) Platelets/Red Cells
5) Platelets/Neutrophils
6) Red Cells/Neutrophils
7) Platelets/Red Cells/Neutrophils

A summary would be made of the number of patients who responded according to each combination of criteria at the Week 12-16 visit which the primary endpoint was measured.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Among 44 enrolled patients in Study ELT112523, one enrolled patient (Patient (b) (6)) was not treated due to a change in diagnosis from aplastic anemia to hypocellular my odysplastic syndrome prior to treatment with eltrombopag. The median duration of follow-up was 7.6 months for 44 enrolled patients. Table 3.1 summarizes the patient disposition as of the clinical cut-off date of Jun 01, 2013.

Table 3.1 Patient Disposition

	Eltrombopag N=44
Patient status, n (%)	
Ongoing in Study	12 (28)
Completed	6 (14)
Died	6 (14)
Not Treated	1 (2)
Withdrawn from Study	19 (44)
Primary reason for study withdrawal, n (%)	
Patient reached protocol defined study withdrawal criteria[b]	14 (33)
Adverse event	2 (5)
Lost to follow-up	1 (2)
Withdrew consent	1 (2)
Lack of efficacy	1 (2)

[Source: Clinical Study Report Table 5]

The demographics of the enrolled population are summarized in Table 3.2.

Table 3.2 Summary of Demographics

	Eltrombopag N=44
Gender, n (%)	
Male	25 (57)
Female	19 (43)
Age (years)	
Median (range)	43.5 (17- 77)
Age, n (%)	
<65	30 (68)
>=65	14 (32)
Race/Ethnicity, n (%)	
Hispanic	10 (23)
White	20 (45)
Asian	1 (2)
Black	13 (30)

The major baseline characteristics of the enrolled population are summarized in Table 3.3

Table 3.3 Summary of Major Baseline Characteristics

	Eltrombopag N=44
Time Since Diagnosis (Months)	
Median (range)	30.9 (10.3-189.8)
Transfused at Referral - Platelets, n (%)	
Yes	40
Number of Platelet Transfusions per Month at Referral	
Median (min-max)	4 (1-9)
RBC Transfusions at Referral	
Yes	38
Number of RBC Transfusions at Referral	
Median (min-max)	4 (1-17)
Transfused at Referral - Platelet & RBC, n (%)	
Yes	36 (82)
Karyotype, n (%)	
Normal	39 (89)
Abnormal	3 (9)
Insufficient metaphases	1(2)

[Source: Clinical Study Report Table 8]

3.2.4 Results and Conclusions

3.2.4.1 Efficacy Results

The date of data-cutoff for the submitted Clinical Study Report (CSR) was June 1, 2013. Table 3.4 summarizes the applicant's and this reviewer's results.

Table 3.4 Results of Response and Duration of Response

	Applicant's Result	**Reviewer's Result**
	Eltrombopag N = 43	**Eltrombopag N =44**
Responder, n (%)	17 (40.0)	17 (38.6)
95% CI (%)	(25, 56)	(24.2, 53.0)
Median (Min-Max) of Duration of Response in Month	3.25 (0.03-41.63)	
Median (95%CI) of Duration of Response in Month		NR*(3.0, NR*)
Responders whose Duration of Response > 12 months, n (%)		6 (35.3)

* *NR=Not reached due to few events (relapse).*

Reviewer's Comments:

2. *The applicant's result was based on 43 patients who received at least one dose of eltrombopag. This reviewer's result was based on 44 patients who were all enrolled in the study; the patient who* was *enrolled but not treated was considered as a non-responder.*
3. *Among 17 responders, there were 3 patients who had relapse while 14 responders still maintained their response as the date of the data cut-off. The reviewer's result of duration of response was obtained by using Kaplan-Meier method with censoring the duration of response at the date of the last assessment for the responders who maintained their response as the date of the data cut-off for the CSR.*
4. *The applicant's result of duration of response was obtained by using the regular summary method without censoring the responders who maintained their response as the date of the data cut-off. The applicant's method is not appropriate for summarizing the duration of response data.*
5. *Per the RAP, the result of secondary endpoint bleeding events would be listed with other adverse events; and the data of another secondary endpoint changes in serum thrombopoietin level would not be included in the study report of ELT112523.*

Table 3.5 summarizes lineage characteristics of hematologic response based on response criteria.

Table 3.5 Lineage Characteristics of Hematologic Response

Response Criteria: Response Due To	Eltrombopag (n=17)
Unilineage, n (%)	**13 (76.5)**
Platelets	7(41)
Red Cells	2(12)
Neutrophils	4(24)
Multi-lineage, n (%)	**4 (23.5)**
Platelets/Red Cells	0
Platelets/Neutrophils	3(18)
Red Cells/Neutrophils	0
Platelets/Red Cells/Neutrophil	1(6)

3.3 Evaluation of Safety

Please refer to Dr. Andrew Dmytrijuk's clinical review for safety evaluation of Promacta®.

3.4 Benefit-Risk Assessment

Whether the results from ELT112523 provide a favorable benefit to risk ratio to support an approval of Promacta® for the proposed indication will be deferred to the clinical review team.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Age, and Race

This reviewer conducted analyses of response rate in the subgroups defined by age (greater than 65 versus less than or equal to 65 years old), gender and race. No subgroup analysis by country or region was conducted since all patients were enrolled in one center in US. Table 4.1 summarizes the analyses in the demographic subgroups.

Table 4.1: Response Rate in the Subgroups

	Eltrombopag N=44
Subgroup	**Responders/Total Patients, n (%)**
Age (year)	
<=65	11/32 (34.4)
>65	6/12 (50.0)
Gender, n	
Male	11/25 (44.0)
Female	6/19 (31.6)
Race/Ethnicity, n	
White	8/20 (40.0)
Hispanic/Latino	7/10 (70.0)
Black/African American	2/13 (15.4)
Asian	0/1(0)

Reviewer's Comments:

6. *As shown in Table 4.1, the response rate in the subgroups except subgroups of black/African American or Asian are consistent with the results in overall population. However, the subgroup analyses results are considered exploratory.*

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

This reviewer found no major statistical issue that impacted the overall conclusions.

5.2 Collective Evidence

Based on the data from 44 enrolled patients in Study ELT112523, the estimated percentage of responders was 38.5% (95% CI: 24.2%, 53.0%). By the time of data cut-off for the final analysis, the median duration of response was not reached with a lower bound of 95% confidence interval of 3.0 months. Fourteen out of 17 responders still maintained their response at the date of the data cut-off for the CSR.

5.3 Conclusions and Recommendations

No statistical comparison was conducted in Study ELT112523 and therefore no statistical inference can be drawn from the study. The nature of single-center Study ELT112523 may not be able to provide a better basis for the subsequent generalization of its findings. However, given the rare disease nature of SAA, whether the adequacy of Study ELT112523 and the results from the study provide a favorable benefit to risk ratio to support an approval of Eltrombopag for the proposed indication will be determined by the clinical review team.

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XIAOPING JIANG
07/31/2014

YUAN L SHEN
08/01/2014

RAJESHWARI SRIDHARA
08/01/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22291Orig1s012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA: 22291 **Submission Dates:** 02/27/2014 and 4/22/2014
SDNs: 456 and 471
Product Name: PROMACTA (eltrombopag) tablets
Sponsor: GlaxoSmithKline
Indication: The treatment of 1) thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy and 2) thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy.
Formulation: Oral Tablet
Submission Type: Efficacy Supplement

Background

PROMACTA is a thrombopoietin receptor agonist indicated for the treatment of 1) thrombocytopenia in patients with chronic and chronic hepatitis C as described above. This submission is an efficacy supplement for the treatment of severe aplastic anemia in patients who have had an insufficient response to immunosuppressive therapy. The proposed initial PROMACTA dose for this proposed indication is 50 mg once daily for most patients. The initial dose should be reduced in patients with hepatic impairment and/or patients of East Asian ancestry. The initial dose should be adjusted to maintain a platelet count greater than ≥50 x 10^9/L. A dose of 150 mg per day should not be exceeded.

Efficacy for the proposed indication was supported by a single-arm, single-center, open-label trial in 43 patients with severe aplastic anemia who had an insufficient response to at least one prior immunosuppressive therapy and who had a platelet count less than or equal to 30 x 10^9/L. The trial reported a response rate of 17% in this population. Pharmacokinetic sampling was not collected in this trial. In addition, the applicant did not submit any other clinical pharmacology related information or analyses in this application. The applicant did propose several grammatical changes to section 12.3 (Pharmacokinetics) of the approved labeling (i.e., changed [redacted] (b) (4) to " compared with" throughout the section (6 instances) and replaced [redacted] (b) (4) with parentheses in one instance).

These proposed labeling changes were evaluated from a clinical pharmacology perspective and are acceptable. We agree with the proposed dose modifications for ethnicity and hepatic impairment because they are consistent with current recommendations under the ITP indication that were based on dedicated pharmacokinetic (PK) trials in these populations. These dedicated trials were submitted and evaluated by the Office of Clinical Pharmacology (OCP) in the original NDA application review (8/11/2008). A dose modification for hepatic impairment is not required for the chronic hepatitis C

indication because it could be justified in a previous efficacy supplement using a population based PK analysis (See 11/05/2012 OCP review).

Recommendation

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology and biopharmaceutics information provided in this efficacy supplement to support a recommendation of approval of PROMACTA for the proposed new indication. The acceptability of specific drug information is provided below.

Decision	Acceptable to OCP?			Comment
Overall	Yes ☒	No ☐	NA ☐	
Evidence of Effectiveness†	Yes ☒	No ☐	NA ☐	1 positive registration trial
Proposed dose for general population	Yes ☒	No ☐	NA ☐	1 positive registration trial at proposed dose
Proposed dose selection for others	Yes ☒	No ☐	NA ☐	Dedicated intrinsic and extrinsic PK trial information is available from the original NDA
Pivotal BE	Yes ☐	No ☐	NA ☒	Addressed in previous OCP review of the original NDA
Labeling	Yes ☒	No ☐	NA ☐	Grammatical changes

†This decision is from a clinical pharmacology perspective only. The overall safety and effectiveness determination is made by the Clinical reviewer.

Signatures

Joseph A. Grillo, Pharm.D.
Reviewer
Division of Clinical Pharmacology 5

Gene Williams, Ph.D.
Team Leader
Division of Clinical Pharmacology 5

Cc: DDOP: CSO - **T Sensie;** MTL - **K Robie-Suh**; MO - **A Dmytrijuk**
DCP-5: Reviewer - **J Grillo;** TL - **G Williams**; Deputy DD - **B Booth;** DD - **A Rahman**

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/s/

JOSEPH A GRILLO
08/01/2014

GENE M WILLIAMS
08/01/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22291Orig1s012

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 7/28/2014

To: Tinya Sensie, Regulatory Project Manager
Division of Hematology Products

From: James Dvorsky, Regulatory Reviewer
Office of Prescription Drug Promotion

Subject: Promacta (eltrombopag) NDA 022291, S-012

We acknowledge receipt of your April 16, 2014, consult request for the proposed product labeling (Package Insert (PI)) for NDA 022291, S-012. We have reviewed the revised draft PI for Promacta and offer our comments below. Please note that OPDP comments are included in the comment bubbles and that the track changes do not reflect our review. Note that this review was based upon the July 28, 2014 version of the label.

35 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JAMES S DVORSKY
07/28/2014

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: July 17, 2014

TO: Tinya Sensie, Regulatory Project Manager
Andrew Dmytrijuk, M.D., Medical Officer
Kathy Robie Suh, M.D., Ph.D., Team Leader
Division of Hematology Products (DHP)

FROM: Anthony Orencia, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 022291/S-012

APPLICANT: GlaxoSmithKline

DRUG: eltrombopag (Promacta®)

NME: No

THERAPEUTIC CLASSIFICATION/REVIEW: priority review

INDICATION: Treatment of adult patients with aplastic anemia previously treated with immunosuppressive therapy

CONSULTATION REQUEST DATE:	April 28, 2014
INSPECTION SUMMARY GOAL DATE:	August 3, 2014
DIVISION ACTION GOAL DATE	August 6, 2014
PDUFA DATE:	August 27, 2014

I. BACKGROUND:

Patients with aplastic anemia who respond to immunosuppressive therapies with an improvement in life-threatening neutropenia may sometimes have persistent thrombocytopenia. Non-responders to immunosuppressive drug therapy, such as anti-thymocyte globulin (ATG) or cyclosporine, and responders with persistent thrombocytopenia may require frequent platelet transfusions and are at risk of serious bleeding complications.

Thrombopoietin is the principal endogenous regulator of platelet production. A thrombopoietin-agonist, eltrombopag (Promacta®) has been shown to increase platelets in healthy subjects and is approved for treatment of thrombocytopenia in patients with chronic immune thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

A single institution federal clinical study site (NIH) addressed the efficacy and safety of eltrombopag in aplastic anemia patients who previously received immunosuppressive therapy.

Study Protocol NIH 09-H-0154/ELT112523
This NIH clinical investigation was a Phase 2, non-randomized, single-arm, open-label study of eltrombopag in aplastic anemia patients with refractory thrombocytopenia following immunosuppressive therapy. The primary objective was to assess the safety and efficacy of the oral thrombopoietin receptor agonist, eltrombopag, in aplastic anemia patients with immunosuppressive therapy refractory thrombocytopenia. The primary endpoint was the proportion of responders as defined by changes in the platelet count and/or platelet transfusion requirements, hemoglobin levels, number of red blood cell transfusions, or neutrophil counts, as measured by International Working Group criteria and the toxicity profile as measured using the Common Terminology Criteria for Adverse Events (CTCAE) criteria.

II. RESULTS:

Name of CI Location	Protocol/Study Site/Number of Subjects Enrolled (n)	Inspection Date	Classification*
Cynthia E. Dunbar National Heart, Lung and Blood Institute/National Institutes of Health Warren Grant Magnuson Clinical Center Bldg 10, CRC CRC 4-5132 9000 Rockville, Pike Bethesda, MD 20892	NIH #09-H-0154/ELT112523 Single Site NDA N=43	June 18-25, 2014	Preliminary: NAI

*Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.
OAI = Significant deviations from regulations. Data unreliable/critical findings may affect data integrity.
Preliminary=The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed, the preliminary designation is converted to a final regulatory classification.

CLINICAL STUDY SITE INVESTIGATOR

1. **Cynthia E. Dunbar, M.D./Protocol NIH 09-H-0154/ELT112523**
   Bethesda, MD

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from June 18 to 25, 2014. A total of 44 subjects were screened and 43 subjects were enrolled. Thirty-five subjects completed the study. An audit of 25 enrolled subjects' records was conducted. Dr. Dunbar was the senior clinical investigator and Ronan Desmond MD, MRCPI was the co-investigator at the time the study was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for these non-randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents

for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:
Data submitted by this clinical site appear acceptable in support of this specific indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For this Phase 2, single-arm, open-label study in support of this NDA, a single clinical site was inspected.

The preliminary regulatory classification for Dr. Dunbar is No Action Indicated (NAI). The study data collected from this clinical site appears reliable in support of the requested indication.

Note: *The inspectional observations noted above are based on preliminary communications with the field investigator and/or preliminary review of the EIR. A clinical inspection summary addendum will be generated, if conclusions on the current inspection report changes significantly, upon receipt the Establishment Inspection Report (EIR). CDER OSI classification of inspection is finalized when written correspondence is issued to the inspected entity (e.g., principal investigator).*

{See appended electronic signature page}

Anthony Orencia, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
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CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H.
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/s/

ANTHONY J ORENCIA
07/17/2014

JANICE K POHLMAN
07/17/2014

KASSA AYALEW
07/21/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22291Orig1s012

RISK ASSESSMENT AND RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Modification Review

Date:	July 1, 2014
Reviewer:	Suzanne Robottom, Pharm.D. Division of Risk Management
Team Leader:	Doris Auth, Pharm.D. Division of Risk Management
Director:	Claudia Manzo, Pharm.D., Acting Director, Office of Medication Error Prevention and Risk Management
Subject:	Review to determine if the communication plan (CP) REMS for Promacta can be released
Drug Name(s):	Promacta (eltrombopag)
Therapeutic Class:	thrombopoietin receptor agonist
Dosage and Route:	25 to 100 mg once daily by mouth
Application Type/Number:	NDA 22291
Applicant/sponsor:	GlaxoSmithKline
OSE RCM #:	2014-785, 594, 805

CONTENTS

EXECUTIVE SUMMARY

This review evaluates the proposed risk evaluation and mitigation strategy (REMS) Modification for Promacta (eltrombopag), NDA 22291 submitted by GlaxoSmithKline (GSK) received on April 23, 2014. GSK requests to eliminate the Promacta REMS, comprised of a communication plan (CP) and timetable for submission of assessments of the REMS. In conjunction with the evaluation of this proposed REMS Modification, this review also considers the current pending prior approval supplement S-012 proposing Promacta for the treatment of cytopenias in patients with severe aplastic anemia.

The Promacta REMS, originally comprised of a Medication Guide (MG), elements to assure safe use (ETASU), an implementation system, and timetable for assessments was initially approved on November 20, 2008. It was modified on December 6, 2011 to remove the MG, ETASU, and implementation system, and to add a CP.

In accordance with CDER's current thinking, elimination of a CP-only REMS may be considered if the CP activities are complete, the REMS assessment indicates that the REMS goals are being met, there are no emerging safety issues, and the team determines that a REMS is no longer necessary to ensure the benefits outweigh the risks. After consideration of these factors, as well as the recent Promacta labeling revisions which have removed or moderated the risks addressed through the REMS, the review team has determined that the REMS is no longer necessary for Promacta to ensure that the benefits of Promacta outweigh the risks. For these reasons, we recommend elimination of the Promacta REMS.

1 INTRODUCTION

This review evaluates the proposed REMS Modification for Promacta (eltrombopag), NDA 22291 submitted by GlaxoSmithKline (GSK) received on April 23, 2014. GSK requests to eliminate the Promacta REMS, comprised of a CP and timetable for submission of assessments of the REMS.

On February 27, 2014, GSK submitted an efficacy supplement for the "treatment of cytopenias in patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy."

As part of evaluating the request to eliminate the REMS, DRISK considered the efficacy supplement currently under review.

1.1 BACKGROUND

Promacta is an orally administered thrombopoietin receptor agonist indicated for:

- treatment of thrombocytopenia in chronic immune (idiopathic) thrombocytopenia (ITP) who have had had an insufficient response to corticosteroids, immunoglobulin, or splenectomy. (approved Nov 20, 2008)
- treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. (approved Nov16, 2012)

As described in our November 18, 2008 REMS review, FDA determined that Promacta was required to have a REMS to ensure that the benefits of the drug outweighed the increased risks of hepatotoxicity, bone marrow fibrosis, serious hemorrhage resulting from worsened thrombocytopenia after cessation of eltrombopag, thromboembolic complications, and an increased risk of hematological malignancies and progression of malignancy in patients with a pre-existing hematological malignancy or myelodysplastic syndrome (MDS). The original REMS included a MG, ETASU, an implementation system, and timetable for assessment. The REMS for Promacta was originally approved on November 20, 2008 coinciding with the initial approval and U.S. marketing of Promacta.

On December 6, 2011 the following modifications to the Promacta REMS program were approved: removal of the MG, ETASU, and implementation system from the REMS and the addition of a CP. At that time, FDA determined that the REMS requirements (ETASU) related to safety data collection were not informative and are no longer necessary to ensure that the benefits of the drug outweigh its risks. FDA concluded that establishing the long-term safety of Promacta is best achieved through ongoing clinical trials, post-approval studies, and post-marketing adverse event reports.comprehensive review and rationale for this modification is provided in other reviews.[1,2,3] Therefore, the most recently approved REMS (December 6, 2011) consists of a CP and a timetable for submission of assessments of the REMS. The CP includes a single Dear Healthcare Provider (DHCP) Letter and Dear Professional Society Letter to be distributed within 15 working days of the REMS (modification) approval. The modified timetable indicates that assessment reports are submitted on June 30th of 2012, 2015, and 2018.

The goal of the modified REMS for Promacta is to inform healthcare providers about the risks of hepatotoxicity, bone marrow reticulin formation and the risk for bone marrow fibrosis, thrombotic/thromboembolic complications, and hematologic malignancies associated with the use of Promacta. These are the same risks addressed in the original REMS with the exception of removing (b) (4) In conjunction with the approval of the REMS modification, the Promacta professional labeling was revised to remove the risk of (b) (4) which prompted removal of this risk from the REMS.

1.2 REGULATORY HISTORY

November 18, 2008: FDA approved Promacta for treatment of thrombocytopenia in patients with ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy with a REMS with elements to assure safe use

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[1] O'Connell K. Thrombopoiesis stimulating Agent REMS. Signed in DARRTS on June 9, 2011 by O'Connell K and Karwoski C.

[2] Recommendation for Elimination of REMS for Promacta. Signed in DARRTS on May 6, 2011 by Dmytrijuk A and again on June 20, 2011 by Kane R and Farrell A.

[3] Robottom S, LaCivita C, O'Connell K, Tavakoli A. Final REMS Modification review to eliminate ETASU. Signed in DARRTS on December 5, 2011 by Robottom S and Karwoski C.

(ETASU; prescriber certification, pharmacy certification, patient enrollment, and documentation of safe use conditions).

July 15, 2009: 1st REMS assessment completed by DRISK

- Based on the initial assessment report, the REMS Assessment review stated that the Promacta REMS appeared to be adequately addressing the first goal and it was premature to assess the second goal regarding establishing the long-term safety and safe use of Promacta.

March 31, 2010: 2nd REMS assessment completed by DRISK

- This assessment did not include survey results and the review explained that "this assessment report meets the basic requirements laid out for the report in the Promacta approval letter."

August 26, 2010: 3rd REMS assessment completed by DRISK

- The REMS assessment review concluded that the assessment was "adequate with comments." The review recommended the educational materials be revised to focus future educational efforts on the risks associated with low survey scores.

February 8, 2011: 4th REMS assessment completed by DRISK

- DRISK Assessment Review recommended opening the discussion period to "address changes in patient and prescriber educational materials and possibly programmatic changes after high level Agency review of whether restricted distribution continues to be necessary…."

February 25, 2011: Conversion from accelerated approval to full approval.

December 6, 2011: FDA approved a REMS Modification to eliminate the ETASU and add a communication plan in conjunction with labeling revisions which removed (b) (4) from labeling.

August 28, 2012: 5th REMS assessment completed by DRISK

- July 19, 2013: REMS Assessment Acknowledgement letter sent to GSK stating that no modifications to the REMS were necessary

November 16, 2012: FDA approved Promacta for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy.

- DHP approved the following labeling revisions to the Warnings and Precautions section:
  - Risk of hematologic malignancies was removed
  - Risk of thrombotic complications was revised
- The REMS was not modified.

February 10, 2014: DHP approved the following labeling revisions to the Warnings and Precautions section:

- Risk of "bone marrow reticulin formation/fibrosis" was removed.
- Risk of hepatotoxicity was revised. Reference to ITP patients was removed from Boxed Warning; Warning revised from hepatotoxicity to "can cause liver enzyme elevations."

February 27, 2014: GSK submitted a prior approval efficacy supplement (S-012) for the "treatment of cytopenias in patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy."

April 23, 2014: GSK submitted a prior approval supplement (S-013) requesting to eliminate the REMS.

2 MATERIALS REVIEWED

- April 23, 2014: Proposed REMS Modification, Supplement 013 (eCTD Sequence No. 0167).
- April 10 2014: approved Promacta Package Insert.
- July 12, 2013: Dmytrijuk A. Memorandum regarding eltrombopag REMS assessment. Signed in DARRTS by Dmytrijuk A and Robie Suh K.
- July 19, 2013: Kane R. REMS Assessment Acknowledgement Letter. Signed in DARRTS by Kane R.
- November 16, 2012: Dmytrijuk A. Clinical review of efficacy supplement 22291/S-008 (treatment of thrombocytopenia in order to initiate antiviral therapy in patients with hepatitis C virus). Signed in DARRTS by Dmytrijuk A and Robie Suh K.
- August 28, 2012: Cvetkovich T. 5th REMS assessment signed in DARRTS by Cvetkovich T and Willy M.

3 RATIONALE FOR PROPOSED REMS MODIFICATION

The applicant requests to eliminate the REMS for Promacta. The request is based on the "additional experience accumulated with Promacta from clinical trials and post-marketing experience since Promacta was approved…, revisions to the safety profile described in the Prescribing Information, and review of the goals of the Promacta REMS." The applicant notes that the communication plan activities were completed in 2012.

Appendix A provides a table listing the risks outlined in the goals of the REMS approved on December 6, 2011 along with the relevant revisions to the labeling regarding those risks since that date. In summary:

- Hematologic malignancies – Warning removed.
- Thrombotic events –Warning revised to target non-ITP patients or patients with risk factors for thromboembolism
- Bone marrow reticulin formation/fibrosis – Warning removed.
- Hepatotoxicity – reference to ITP patients removed from Boxed Warning; Warning revised from hepatotoxicity to "can cause liver enzyme elevations."

4 DISCUSSION

4.1 CRITERIA FOR ELIMINATING A CP-ONLY REMS

CDER's current thinking is to consider the following conditions when deliberating if a proposed REMS modification to eliminate a CP-only REMS is a reasonable option[4]:

1. All activities for the CP have been completed, and/or the CP activities have been assessed at least once; and

2. If the CP has been assessed, the goal of the CP has been met and there is no need to further assess the current CP; If the CP has not been assessed, no assessment of the current CP is necessary; and

3. There are no identified or emerging safety issues that may require continued or new communication within the next 6 months; and

4. If the REMS include elements to assure safe use (ETASU) removal of CP has no implications for those elements.

5. The communication plan is no longer necessary as an element of the REMS to ensure that the benefits of the drug outweigh the risks.

4.2 ASSESSMENT OF WHETHER A REMS IS STILL NECESSARY

Below is DRISK's analysis of whether a REMS can be eliminated taking into account the conditions of eliminating a CP-only REMS.

1. All activities for the CP have been completed, and the CP activities have been assessed at least once:

   Reviewer comment: The tools for the Promacta CP REMS include a DHCP letter and Dear Professional Society letter.

   (b) (4)

   [redacted]

   A Dear Professional Society letter was sent on December 9, 2011 to the leadership of the professional societies outline din the REMS. No letters were returned.

   Both letters were posted on the GSK website, www.promactacares.com, from December 6, 2011 through June 30, 2012 at which time GSK decommissioned the website.

[4] Safety Requirements Team Update: Checklist for eliminating a CP-only REMS, December 18, 2013

The execution of the CP was completed immediately after the REMS modification was approved and no additional REMS communications were required based on requirements set forth in the REMS approved on December 6, 2011 and the June 29, 2012 REMS assessment report. This assessment report included data on the CP activities as well as an evaluation of HCP understanding of the risks as described below.

2. If the CP has been assessed, the goal of the CP has been met and there is no need to further assess the current CP; If the CP has not been assessed, no assessment of the current CP is necessary:

   Reviewer comment: Per the modified REMS approved on December 6, 2011, the goal of the Promacta REMS is to inform healthcare providers about the risks of hepatotoxicity, bone marrow reticulin formation and the risk for bone marrow fibrosis, thrombotic/thromboembolic complications, and hematologic malignancies associated with the use of Promacta.

   The Promacta REMS assessment plan includes:

   a) An evaluation of HCPs' understanding of the risks of Promacta (eltrombopag)

   b) With regard to assessment of the communication plan:

   - *The date(s) of the launch of the communication plan*
   - *The number of recipients of the direct mail to Dear Healthcare Professional Letter (DHCPL)*
   - *The number of electronic DHCP letters opened*
   - *The number of direct mailings returned*
   - *The sources of the recipient lists*
   - *The number of Dear Professional Society letters sent*
   - *The number of Dear Professional Society letters returned*

   The timetable for submission of assessments is June 30, 2012, 2015, and 2018.

   With regard to the evaluation of the HCPs' understanding of the risks of Promacta, the results of the question pertaining to risks associated with Promacta are provided below as presented by the applicant in the most recent REMS assessment report (June 30, 2012). The survey question is followed by results from each of the three surveys (called Waves I, II, and III) that have been conducted. In addition, the results from the Wave III survey are stratified by prescribers who had been registered in the REMS, and those who had not previously been registered.

Table II-3
Risks Associated with PROMACTA (Q3)
According to the prescribing information, which of the following risks may be associated with PROMACTA?

	Wave I		Wave II		Wave III Total	Wave III Prev. Reg.		Wave III Not Reg.
(n) =	(104)		(163)		(400)	(200)		(200)
% Answering:	%		%		%	%		%
Bone Marrow Reticulin and Risk for Bone Marrow Fibrosis	91	>	82	>	69	81	>	58
Hepatoxicity/Hepatic Effects	68		63	>	50	58	>	43
Thrombotic/Thromboembolic Complications	58		54		48	55	>	42
Hematologic Malignancies and Progression of Hematologic Malignancies	24		24		26	29		23
Anaphylaxis	15		19		14	19	>	10
Stevens-Johnson Syndrome	11		14		9	11		7
Don't Know / Not Sure*	--		--		11	3	<	19

*Not presented in Wave I or II.

These survey results revealed that responders did not demonstrate optimal understanding of the risks. However, DHP conveyed that the severity of these risks as described in current 2011 approved labeling required re-evaluation.

- *In a November 16, 2012[5] review Dr. Dmytrijuk recommended revisions to remove the hematologic malignancy Warning and revisions to the thrombotic complications Warning. Those labeling changes were approved on November 16, 2012.*
- *In a July 12, 2013[6] review Dr. Dmytrijuk stated that that based on the "totality of evidence to date, the hepatotoxicity concern for patients with ITP who are treated with eltrombopag does not appear to rise to a level requiring a warning". Dr. Dmytrijuk also concluded that there does not appear to be an increased risk for myelofibrosis or significant hepatotoxicity in patients with ITP who are treated with eltrombopag." On February 10, 2014, revised labeling was approved which removed bone marrow reticulin formation/fibrosis from the Warnings section and*

[5] Dmytrijuk A. Clinical review of efficacy supplement 22291/S-008 (treatment of thrombocytopenia in order to initiate antiviral therapy in patients with hepatitis C virus). Signed in DARRTS on November 16, 2012 by Dmytrijuk A and Robie Suh K.

[6] Dmytrijuk A. Memorandum regarding eltrombopag REMS assessment. Signed in DARRTS on July 12, 2013 by Dmytrijuk A and Robie Suh K.

revised the hepatotoxicity Boxed Warning and Warning to focus on non-ITP patients.

Therefore, further communications to prescribers about these risks were not warranted because the risk profile has changed and a REMS is no longer necessary.

3. There are no identified or emerging safety issues that may require continued or new communication within the next 6 months:

Reviewer comment: The Division of Pharmacovigilance (DPV) was consulted via email on June 16, 2014 regarding any new or emerging safety issues that may require continued or new communication. DPV is in the process of finalizing (b) (4) (b) (4) (b) (4) *section of the label but no additional communication regarding this risk is being proposed or anticipated.*

Members from DRISK and the Division of Hematology Products (DHP) met on March 12, 2014 to discuss if the REMS for Promacta could be eliminated based on the completion of the communication plan activities and labeling revisions. It was noted that an efficacy supplement for the treatment of patients with severe aplastic anemia was under review. During the meeting, DHP identified no additional emerging safety issues with the current indications or the aplastic anemia indication. Moreover, DHP identified no new or emerging safety issues since the March 12, 2014 meeting.

DRISK considered whether additional risk mitigation beyond labeling would be necessary for the severe aplastic anemia indication under review. Based on the safety analysis presented at the Mid-Cycle Meeting on May 27 2014, the safety findings are similar in the aplastic anemia population compared to the current approved labeling. We would not expect that the prescribing population to change or broaden with the addition of this indication.

4. If the REMS include elements to assure safe use (ETASU) removal of CP has no implications for those elements:

Reviewer comment: The Promacta REMS does not include ETASU therefore this does not apply.

5. The communication plan is no longer necessary as an element of the REMS to ensure that the benefits of the drug outweigh the risks.

Reviewer comment: The benefit risk profile of Promacta has evolved since its initial approval in 2008 prompting removal of several of the risks from labeling and significant revision to moderate the remaining risks addressed through the REMS. Therefore, a communication plan is no longer necessary as an element of the REMS to ensure that the benefits of Promacta outweigh the risks.

5 CONCLUSION AND RECOMMENDATION

The review team concluded that the CP activities are complete (as of July 2012), the labeling has been revised; removing or moderating the risks addressed in the REMS, and that there are no identified or emerging safety issues that may require continued or new communication. DHP review of the efficacy supplement has not identified any new safety issues. Therefore, the team has determined that the REMS is no longer necessary for Promacta to ensure that the benefits of Promacta outweigh the risks. For these reasons, we recommend elimination of the Promacta REMS and releasing GSK from the REMS requirements for Promacta.

Attachment: Appendix A

Appendix A: Labeling Revisions by date approved for Promacta (eltrombopag)

Promacta Risk addressed in the REMS	Dec 6, 2011	Nov 16, 2012	2014[1]
Hepatotoxicity	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.	No change	Revised Boxed Warning: In patients with chronic hepatitis C, PROMACTA in combination with interferon and ribavirin may increase the risk of hepatic decompensation.
	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. One patient in the placebo group experienced a Grade 4 liver test abnormality. Overall, serum liver test abnormalities (predominantly Grade 2 or less in severity)	Revised 5.1 Hepatotoxicity PROMACTA may cause hepatotoxicity. In the controlled clinical studies in chronic ITP, 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	Revised 5.1 Hepatic decompensation in Patients with chronic hepatitis C 5.2 Hepatotoxicity PROMACTA can cause liver enzyme elevations [see Adverse Reactions (6.1)]. 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.

[1] The most recent label was approved on April 10, 2014 which included changes to Section 12.3 (Pharmacokinetics). No changes to the Warnings and Precautions sections were approved. The most recent changes to the Warnings and Precautions section were those approved on February 10, 2014.

	were reported in 11% and 7% of the PROMACTA and placebo groups, respectively. In the 3 controlled studies, four patients (1%) treated with PROMACTA and three patients in the placebo group (2%) 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 treatment with PROMACTA 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. Pharmacokinetic evaluations in patients with hepatic impairment show that plasma eltrombopag AUC(0-□) increases with increasing degree of hepatic impairment (as measured by Child-Pugh). Exercise caution when administering PROMACTA to patients with hepatic	disease, and death. One patient in the placebo group experienced a Grade 4 liver test abnormality. Overall, serum liver test abnormalities (predominantly Grade 2 or less in severity) were reported in 11% and 7% of the PROMACTA and placebo groups, respectively. In the 3 controlled chronic ITP studies, four patients (1%) treated with PROMACTA and three patients in the placebo group (2%) 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 trial. Six of these patients again experienced liver test abnormalities (predominantly Grade 1) resulting in discontinuation of PROMACTA in one patient. In the extension chronic ITP trial, one additional patient had PROMACTA discontinued due to liver test abnormalities (≤Grade 3). In 2 controlled clinical studies in patients with chronic hepatitis C and thrombocytopenia, ALT or AST ≥3X ULN was reported in 34% and 38% of the PROMACTA and placebo groups, respectively. Most patients receiving PROMACTA in combination with peginterferon/ribavirin therapy will experience indirect hyperbilirubinemia. Overall, total bilirubin ≥1.5 X ULN was reported in 76% and 50% of patients receiving PROMACTA and placebo, respectively. 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	PROMACTA inhibits UGT1A1 and OATP1B1, which may lead to indirect hyperbilirubinemia. 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 resolved or stabilized. Discontinue PROMACTA if ALT levels increase to ≥3X ULN in patients with normal liver function or ≥3X baseline in patients with pre-treatment elevations in transaminases and are: • progressively increasing, or • persistent for ≥4 weeks, or • accompanied by increased direct bilirubin, or • accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation. If the potential benefit for reinitiating treatment with PROMACTA is considered to outweigh the risk for hepatotoxicity, then consider cautiously reintroducing PROMACTA and measure serum liver tests weekly during the dose adjustment phase. Hepatotoxicity may reoccur if PROMACTA is reinitiated. If liver tests abnormalities persist, worsen or recur, then permanently discontinue PROMACTA.

	impairment (Child-Pugh Class A, B, C). Use a lower starting dose of PROMACTA in patients with any degree of hepatic impairment and monitor closely [see Dosage and Administration (2.1) and Use in Specific Populations (8.6)].	levels increase to ≥3X ULN in patients with normal liver function or ≥3X baseline in patients with pre-treatment elevations in transaminases 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 treatment with PROMACTA 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. [added] 5.2 Hepatic Decompensation in Patients with chronic Hepatitis C	
Bone marrow reticulin/fibrosis	PROMACTA may increase the risk for development or progression of reticulin fiber deposition within the bone marrow. In the extension study, 151 patients have had bone marrow biopsies evaluated for increased reticulin and collagen fiber deposition. Bone marrow biopsies taken after 1 year of therapy showed predominantly myelofibrosis (MF) Grade 1 or less in 140/151 (93%) of patients. There were 11/151 (7%) of patients with MF Grade 2. Four patients had collagen deposition reported. One patient with a pre-existing MF Grade 1 developed a MF Grade 2 and subsequently discontinued treatment with PROMACTA. Clinical studies have not excluded a risk of bone marrow fibrosis with clinical consequences. If new or worsening blood morphological abnormalities or	Revised PROMACTA may increase the risk for development or progression of reticulin fiber deposition within the bone marrow. In the extension trial in chronic ITP, 151 patients have had bone marrow biopsies evaluated for increased reticulin and collagen fiber deposition. Bone marrow biopsies taken after 1 year of therapy showed predominantly myelofibrosis (MF) Grade 1 or less in 140/151 (93%) of patients. There were 11/151 (7%) of patients with MF Grade 2. Four patients had collagen deposition reported. One patient with a pre-existing MF	Removed

	cytopenias occur, consider a bone marrow biopsy including staining for fibrosis.	Grade 1 developed a MF Grade 2 and subsequently discontinued treatment with PROMACTA. Clinical studies have not demonstrated clinical consequences to date. If new or worsening blood morphological abnormalities or cytopenias occur, consider a bone marrow biopsy including staining for fibrosis.	
Thrombotic complications	Thrombotic/thromboembolic complications may result from increases in platelet counts with PROMACTA. Reported thrombotic/thromboembolic complications included both venous and arterial events and were observed at low and at normal platelet counts. Consider the potential for an increased risk of thromboembolism when administering PROMACTA to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, chronic liver disease). 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 as necessary to decrease the risk for bleeding *[see Dosage and Administration (2.2)]*. In a controlled study in non-ITP thrombocytopenic patients with chronic liver disease undergoing elective invasive procedures (N = 292), the risk of thrombotic events was increased in patients treated with 75 mg PROMACTA once daily. Seven thrombotic complications (six patients) were reported in the group that received PROMACTA and three thrombotic complications were reported in the placebo group (two patients). All of the thrombotic complications reported in the group that received PROMACTA were of the portal venous system. Five of the six patients in the group that received PROMACTA experienced a thrombotic complication within 30 days of completing treatment with PROMACTA and at a platelet count above 200 x 109/L. The risk of portal venous thrombosis was increased in	Revised In 2 controlled clinical trials in patients with chronic hepatitis C and thrombocytopenia, 3% (31/955) treated with PROMACTA experienced a thrombotic event compared to 1% (5/484) on placebo. The majority of events were of the portal venous system (1% in patients treated with PROMACTA versus <1% for placebo). Thrombotic/thromboembolic complications may result from increases in platelet counts with PROMACTA. Reported thrombotic/thromboembolic complications included both venous and arterial events and were observed at low and at normal platelet counts. Consider the potential for an increased risk of thromboembolism when administering PROMACTA to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, chronic liver disease). 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 target platelet counts [see Dosage and Administration (2.1, 2.2)]. In a controlled trial in non-ITP thrombocytopenic patients with chronic liver disease undergoing elective invasive procedures (N = 292), the risk of thrombotic events was increased in patients treated with 75 mg PROMACTA once daily. Seven thrombotic complications (six patients) were	No change

	thrombocytopenic patients with chronic liver disease treated with 75 mg PROMACTA once daily for 2 weeks in preparation for invasive procedures. Exercise caution when administering PROMACTA to patients with hepatic impairment (Child-Pugh Class A, B, C). Use a lower starting dose of PROMACTA in patients with any degree of hepatic impairment and monitor closely [see Dosage and Administration (2.1)]. PROMACTA is not indicated for the treatment of thrombocytopenia in patients with chronic liver disease.	reported in the group that received PROMACTA and three thrombotic complications were reported in the placebo group (two patients). All of the thrombotic complications reported in the group that received PROMACTA were portal vein thrombosis (PVT). Symptoms of PVT included abdominal pain, nausea, vomiting, and diarrhea. Five of the six patients in the group that received PROMACTA experienced a thrombotic complication within 30 days of completing treatment with PROMACTA and at a platelet count above 200 x 10^9/L. The risk of portal venous thrombosis was increased in thrombocytopenic patients with chronic liver disease treated with 75 mg PROMACTA once daily for 2 weeks in preparation for invasive procedures	
Hematologic 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 months. During this period no hematologic malignancies were reported in patients treated with PROMACTA. One hematologic malignancy (non-Hodgkin's lymphoma) was reported in the extension study. PROMACTA is not indicated for the treatment of thrombocytopenia due to diseases or treatments that cause thrombocytopenia (e.g., myelodysplasia or chemotherapy) other than chronic ITP.	Removed	

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/s/

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