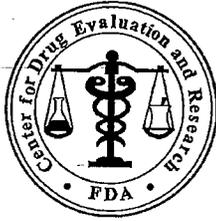


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 22-291

**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**

Date: November 20, 2008

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Subject: Review of Risk Evaluation and Mitigation Strategy (REMS)

Drug Name(s): Promacta (eltrombopag)

Application Type/Number: NDA 22-291

Applicant/sponsor: GSK

OSE RCM #: 2008-414

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EXECUTIVE SUMMARY

Eltrombopag (Promacta) is an oral thrombopoietin receptor agonist that interacts with the transmembrane domain of the thrombopoietin receptor, inducing the proliferation and differentiation of megakaryocytes. The signaling cascade is similar, but not identical to, that of endogenous thrombopoietin. The Sponsor submitted a proposed risk management program (RMP) with the NDA that inadequately addressed the risks associated with eltrombopag and the proposed limitations to the indication ("short-term (6 week) treatment of previously treated adults with chronic ITP to increase platelet counts and reduce or prevent bleeding"). These risks include 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). OSE's concerns regarding the proposed RMP were addressed in the OSE briefing document for the May 30, 2008 Oncologic Drugs Advisory Committee (ODAC) Meeting. Based on the ODAC discussion, similar risk concerns to the first and only other thrombopoietin receptor agonist, romiplostim (Nplate), and subsequent FDA internal discussions, it was determined that a Risk Evaluation and Mitigation Strategy (REMS) was necessary to ensure that the benefits of eltrombopag treatment exceed the risks. The REMS, titled, Promacta CARES Program (no acronym), submitted on November 18, 2008, includes a Medication Guide, Elements to Assure Safe Use, an Implementation Plan, and timetable for assessment with the information needed for assessment.

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1 BACKGROUND

1.1 INTRODUCTION

Romiplostim is a second-in-class thrombopoietin receptor agonist. The indication under consideration for approval is identical to the approved indication for Nplate - "treatment of thrombocytopenia in patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Promacta should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding. Promacta should not be used in an attempt to normalize platelets." In conjunction with data from an open-label extension study, ongoing controlled trial (RAISE), along with the risk of serious hemorrhage upon drug discontinuation, it appeared impractical to approve eltrombopag for short-term treatment for a chronic condition. Therefore, DMIHP chose to recommend modification to the originally submitted short-term indication and approval under Subpart H.

The proposed dosing regimen is 50 mg once daily by mouth. Dosing is titrated weekly to maintain a platelet count $\geq 50 \times 10^9/L$. The maximum dose is 75 mg once daily. This mechanism of action and once daily oral dosing makes eltrombopag appealing for broad use in a variety of diseases associated with thrombocytopenia. Studies are ongoing for the use of eltrombopag for long-term treatment of ITP, treatment of thrombocytopenia secondary to cirrhosis associated with hepatitis C, and chemotherapy-induced thrombocytopenia.

The ODAC convened on May 30, 2008 to consider the eltrombopag application for short-term use. The OSE briefing document for the Advisory Committee meeting is presented in Appendix A. The Committee concluded unanimously that the clinical data demonstrated a favorable risk-benefit profile for "short-term" treatment of patients with chronic ITP. Overall, the Committee

agreed that in order to assure safe use of eltrombopag, a risk management plan should be put in place.¹

2 METHODS AND MATERIALS

2.1 DATA AND INFORMATION SOURCES

The following risk management submissions for Promacta were reviewed:

- Amendment 26; August 5, 2008
 - FDA comments provided via email on August 25, 2008 (available in DFS)
- Amendment 30; September 15, 2008 (provided via email on September 4, 2008)
 - FDA comments provided via email on September 22, 2008 and discussed in September 22, 2008 teleconference with GSK (available in DFS)
- Amendment 35; October 1, 2008 (provided via email on September 25, 2008)
 - FDA comments provided via email on October 14, 2008(available in DFS)
- Amendment 39; October 21, 2008
 - FDA comments provided via email on October 30, 2008(available in DFS)
- Amendment 41; November 4, 2008
 - FDA comments provided via email on November 4, 2008(available in DFS)
- Amendment 42; November 18, 2008 (final REMS Submission)

2.2 ANALYSIS TECHNIQUES

Each risk management submission was reviewed for responsiveness to FDA comments. The need for a REMS was communicated to the Sponsor in the July 10, 2008 face-to-face meeting. The November 18, 2008 GSK submission was reviewed for conformity to the Food and Drug Administration Amendments Act of 2007 (FDAAA) section 505-1 titled, "Risk Evaluation and Mitigation Strategies."

3 RESULTS OF REVIEW

3.1 CONSIDERATION OF REMS

- **The estimated size of the population likely to use the drug involved.**

The prevalence rate of chronic (adult) immune thrombocytopenic purpura (ITP) ITP was estimated at 24 cases per 100,000 persons or 52,700 adult cases in the United States based on the 2005 census estimates. This prevalence (published in International Society on Thrombosis and Haemostasis by Feudjo-Tepie et al in 2008) was based upon analyses of the Integrated Healthcare Information System (IHCIS) database, one of the largest US health care managed databases. McMillan (Ann Intern Med: 1997) estimates that 30% of chronic ITP cases are "refractory" and this subset is the group of patients who are most

¹ Summary Minutes for the May 30, 2008 Oncologic Drugs Advisory Committee meeting.
<http://www.fda.gov/ohrms/dockets/ac/08/minutes/2008-4366m1-Final.pdf> Accessed November 17, 2008.

likely to receive romiplostim. Hence, approximately 16,000 patients in the US (based on 2005 census) are general candidates for romiplostim therapy, as indicated.²

- **The seriousness of the disease or condition being treated by the drug.**

Eltrombopag is indicated to treat a very serious stage of chronic ITP that is generally regarded as so serious that patients are at imminent risk of death due to hemorrhage.²

- **The expected benefit of the drug with respect to such a disease or condition**

Eltrombopag has been shown to be effective in 60 to 70% of treated chronic ITP patients. This treatment effect is a remarkable response since these patients had failed most (if not all) prior therapies. The specific treatment benefit is an increase in blood platelet counts to a level that lessens the risk for serious hemorrhage.²

- **The expected actual duration of treatment with the drug.**

Eltrombopag therapy is anticipated as life-long (many years) therapy for many patients. The indication will specifically identify patients with chronic ITP who have had insufficient response to other treatments. This sub-population is one that generally has no other long term therapeutic options and chronic ITP rarely spontaneously resolves.²

- **The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.**

The serious adverse events signaled in the clinical development of eltrombopag are risks for hepatotoxicity and risk for hemorrhage following discontinuation of eltrombopag due to worsened thrombocytopenia than was present at baseline. Hepatotoxicity is not an event with an established background incidence in patients with chronic ITP. Hence, hepatotoxicity in the eltrombopag development program provides strong evidence of a drug-related effect.

Eltrombopag also has potentially serious risks due to the risks associated with other members of the class of thrombopoietin products. These risks include the following: a risk for hematologic malignancy due to stimulation of the thrombopoietin receptor (a risk supported by *in vitro* studies); a risk for thrombotic/thromboembolic risks associated with excessive platelet counts (as may occur either due to medication errors or as patient-specific responses to the drug) as well as a risk for bone marrow fibrosis (as documented by animal studies of thrombopoietin receptor products).

The background incidence of hematologic malignancy, bone marrow fibrosis or thrombosis in chronic ITP is not known, since most patients either respond to initial therapy with prednisone or require more aggressive immunosuppressive medications or splenectomy and these therapies may alter the risks. In a long term (median of 92 months), follow-up study of 402 patients who underwent splenectomy (the patient population potentially at greatest risk for malignancy or marrow fibrosis), only 2% of patients experienced thromboses, malignancy occurred in 3%, and marrow fibrosis was not reported (Haematologica 2005: 90 (1); Vianelli et al). Together these data suggest

² Rieves, D, Division Director Decisional Review Memorandum for the Promacta Risk Evaluation and Mitigation Strategy dated November 4, 2008.

that the risk for marrow fibrosis, malignancy and thrombosis are relatively low within the subset of patients who undergo splenectomy for chronic ITP.

- **Whether the drug is a new molecular entity.**

Eltrombopag is a new molecular entity and will be the second member of the class of thrombopoietin mimetic agents approved by the FDA.²

In summary, eltrombopag has shown to be effective for the treatment of thrombocytopenia associated with chronic ITP in patients who have had an insufficient response to other treatments and it fulfills an unmet need for this specific ITP sub-population. However, there are serious safety concerns that require careful consideration, regular re-evaluation of the benefit risk for each patient, and long-term, periodic follow-up throughout the treatment course with eltrombopag. A REMS is required to make certain that the use of eltrombopag coincides with periodic re-evaluation and safe use assessment to ensure that the benefit of treatment of chronic ITP with eltrombopag exceed the risks of hepatotoxicity, bone marrow reticulin formation and bone marrow fibrosis, serious hemorrhage due to worsened thrombocytopenia after cessation of eltrombopag, thromboembolic complications, and increased risk of hematological malignancies and progression of malignancy in patients with a pre-existing hematological malignancy or myelodysplastic syndrome.²

3.2 PROPOSED REMS

3.2.1 Goals

The REMS includes the following goals:

- To promote informed risk-benefit decisions before initiating treatment and while patients are on treatment to ensure appropriate use of Promacta (eltrombopag)
- To establish the long-term safety and safe use of Promacta (eltrombopag) through periodic monitoring of all patients who receive Promacta (eltrombopag) for hepatotoxicity, changes in bone marrow reticulin formation and bone marrow fibrosis, worsened thrombocytopenia and increased hemorrhage risk after cessation of Promacta, thrombotic/thromboembolic complications, and malignancies and progression of malignancy.

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3.2.2 REMS Elements

The REMS includes a Medication Guide, Elements to Assure Safe Use, an Implementation Plan, and timetable for assessment with the information needed for assessment. These are each described below. The final REMS is presented in Appendix B.

3.2.2.1 Medication Guide

Sponsor must provide a Medication Guide to pharmacists to be provided to patients each time PROMACTA is dispensed to increase the patient's knowledge of how to safely and effectively use PROMACTA. GSK must provide 3 copies of the Medication Guide for each unit of use bottle, in case the pharmacist dispenses less than 30 tablets from the bottle.

All authorized pharmacies must provide a Medication Guide each time they dispense PROMACTA to a patient. As part of the pharmacy authorization agreement, pharmacies must agree to provide a Medication Guide each time they dispense the drug.

3.2.2.2 Communication Plan

A Communication Plan is not part of the Promacta REMS Program. All materials needed for the implementation of this REMS are included under the respective Element to Assure Safe Use.

3.2.2.3 Elements to Assure Safe Use

The Promacta REMS includes the following elements to assure safe use:

A. Promacta will only be prescribed by healthcare providers who are specially certified under 505-1(f)(3)(A)

PROMACTA CARES requires prescribers to be certified and enrolled in PROMACTA CARES before they can prescribe PROMACTA. To become certified prescribers must complete the one-time Prescriber Enrollment Form and fax the form to PROMACTA CARES. The prescriber must receive the Prescriber Enrollment Confirmation Letter, via fax to confirm the prescriber's enrollment into PROMACTA CARES.

Certification of prescribers into the Nplate NEXUS Program requires prescribers to enroll in the Promacta CARES Program and attest to safe use conditions. The following materials support the certification process:

- Dear Prescriber/Healthcare Provider Introduction Letter
- PROMACTA CARES Enrollment Procedure
- PROMACTA CARES Compliance Monitoring Procedure
- PROMACTA CARES Enrollment Folder
- PROMACTA CARES Overview Booklet
- PROMACTA CARES Prescriber Enrollment Form
- PROMACTA CARES Prescriber Enrollment Confirmation Letter
- PROMACTA CARES Call Center
- PROMACTA CARES Instructional Video
- PROMACTA CARES Website (www.PROMACTACARES.com)

B. Promacta will only be dispensed by pharmacies and healthcare settings under 505-1(f)(3)(C) (i.e., pharmacies in hospitals/institutions and physician dispensing clinics) that are specially certified under 505-1(f)(3)(B).

GSK has designed a controlled distribution system to deliver PROMACTA to select certified pharmacies including: specialty pharmacies, hospital pharmacies, and other healthcare settings (such as physician practices dispensing medication in accordance with state regulations, ambulatory treatment/infusion centers). PROMACTA will not be available to non-institutional retail pharmacies. Promacta will only be distributed to certified pharmacies and healthcare settings via a drop ship program through which GSK must maintain direct control over who purchases Promacta. The certified dispensing entity may order PROMACTA through their usual distributor; the distributor will transmit the order to the PROMACTA CARES Program.

Certified pharmacies and healthcare settings can only dispense PROMACTA if they are enrolled in PROMACTA CARES. To enroll, the pharmacy and/or healthcare setting must complete the one-time Pharmacy Authorization and fax the form to PROMACTA CARES. The pharmacy and/or healthcare setting must receive a Pharmacy Authorization Confirmation

Letter, via fax from the PROMACTA CARES to confirm that the pharmacy and/or healthcare setting is authorized to dispense PROMACTA.

To become a certified pharmacy, a recognized signatory authority for the pharmacy (e.g., pharmacy director, director of drug information, P&T Committee chair) must complete the Pharmacy Authorization Form and attest to safe use conditions.

The following materials support the certification process:

- Dear Pharmacist Introduction Letter
- Dear Managed Care, Wholesaler, Distributor, and Specialty Pharmacy Customer Introduction Letter
- PROMACTA CARES Enrollment Procedure
- PROMACTA CARES Controlled Distribution Procedure
- PROMACTA CARES Compliance Monitoring Procedure
- Inventory Tracking Log for Promacta
- PROMACTA CARES Overview Booklet
- PROMACTA CARES Specialty Pharmacy Authorization Form
- PROMACTA CARES VA Pharmacy Authorization Form
- PROMACTA CARES Hospital Pharmacy and Dispensing Clinic Authorization Form
- PROMACTA CARES Pharmacy Authorization Confirmation Letter
- PROMACTA CARES Call Center
- PROMACTA CARES Instructional Video
- PROMACTA CARES Website (www.PROMACTACARES.com)

C. Each patient treated with Promacta is enrolled in PROMACTA CARES for documentation of safe-use conditions under 505-1(f)(3)(D)

Patients are enrolled into the Promacta CARES Program by their prescriber before initiating Promacta treatment. Part of the enrollment requires patients to attest to understanding the risks, reporting adverse events to their prescriber, and understanding that in order to receive Promacta, they will be automatically enrolled in the Promacta CARES Program so their healthcare provider can continually evaluate the appropriateness of continuing Promacta and report adverse events to GSK.

The prescriber must receive Patient Enrollment Confirmation Letter, via fax from PROMACTA CARES to confirm the patient's enrollment into PROMACTA CARES. The letter provides the unique patient ID number (PID#) assigned to the patient.

The following materials support the certification process:

- PROMACTA CARES Enrollment Procedure
- PROMACTA CARES Patient Enrollment Form
- PROMACTA CARES Patient Enrollment Confirmation Letter
- PROMACTA CARES Patient Overview Sheet
- PROMACTA CARES Website (www.PROMACTACARES.com)
- PROMACTA CARES Call Center

D. Each patient treated with PROMACTA is subject to certain monitoring under 505-1(f)(3)(E)

Prescribers must complete the Promacta CARES Program Patient Baseline Form for each patient within 30 days of enrollment and a Medical Follow-up and Authorization Form

every six months during treatment with Promacta. The Medical Follow-up and Authorization Form also requires the prescriber to authorize continued treatment with Promacta. The Medical Follow-Up and Authorization Form includes specific questions about the following risks:

- Hepatotoxicity
- Thrombosis/thromboembolism
- Hematological malignancy
- MDS
- Bone marrow reticulin formation
- Bone marrow fibrosis

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The Promacta CARES Program Call Center will remind the Promacta prescriber when it is time to complete the questionnaires for each patient. All reported serious adverse events will be further investigated and followed by GSK. In addition, risk-specific follow-up forms were developed to address the above mentioned risks and facilitate more consistent data collection.

The pharmacy must verify that the patient and prescriber are enrolled in Promacta and that the patient is eligible to receive Promacta prior to dispensing Promacta by calling the Promacta CARES Call Center. The Promacta CARES Program provides a unique verification number for each prescription/refill dispensed. This verification number must be recorded on the Inventory Tracking Log for each patient to ensure prescriber and pharmacy compliance with the REMS program.

At the time the prescriber determines that a patient should be discontinued from Promacta, the Promacta CARES Program Discontinuation and Post-Discontinuation Follow-up Form must be completed at the time of discontinuation and 3 months later. The form includes a question to address the risk of worsening thrombocytopenia and risk of serious bleeding.

The following materials support the monitoring component:

- PROMACTA CARES Long-term Monitoring Procedure
- Patient Baseline Form
- Medical Follow-up and Authorization Form
- Patient Reauthorization Confirmation Letter
- Discontinuation and Post-Therapy Form
- Patient Discontinuation Letter
- Risk specific targeted follow up questionnaires
 - Bone Marrow Reticulin/Bone Marrow Fibrosis
 - Hepatobiliary Laboratory Abnormalities
 - Hematological Malignancy
 - Worsening Thrombocytopenia and Bleeding
 - Thrombotic/Thromboembolic Events
- Re-enrollment Post-Discontinuation due to Hepatotoxicity Letter #1
- Re-enrollment Post-Discontinuation due to Hepatotoxicity Letter #2
- Inventory Tracking Log for Promacta

3.2.2.4 Implementation System

The REMS also includes an Implementation System to monitor and evaluate implementation of some of the elements to assure safe use.

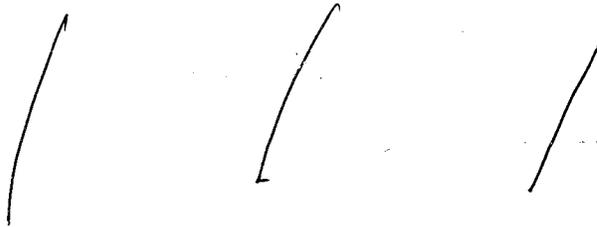
3.2.2.5 Assessment of REMS

The Sponsor will submit a REMS Assessment to FDA every 6 months for the first 24 months following approval, then annually (from REMS approval date) thereafter.

The REMS Assessments will include the following information (more details are provided in Appendix C):

- An assessment of enrollment and discontinuation statistics for patients, prescribers, and institutions
- A narrative summary with analysis of patients who discontinued Promacta treatment including duration of treatment and the reason for discontinuation during the reporting period
- _____
- A narrative summary with analysis of reports with inpatient to outpatient (or vice versa) transition issues
- An assessment of use data establishing the circumstances of the use of Promacta
- An assessment of prescriber compliance with requirements of the REMS
- An assessment of pharmacy compliance with requirements of the REMS

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- A summary and analysis of unintended interruptions in treatment (e.g., interruptions due to shipment delays and other logistical issues). This summary should describe any corrective actions taken.
- _____
- A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
- An assessment of healthcare provider and patient understanding regarding the safe-use of Promacta (i.e., the results of surveys administered to prescribers and patients).

3.3 PROPOSED PHARMACOVIGILANCE PLAN

On November 4, 2008, Amgen agreed to expedited reporting of bone marrow fibrosis, and new malignancy/malignancy progression.

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4 DISCUSSION

The sponsor has proposed a REMS that requires prescriber, pharmacy, and patient enrollment with patient monitoring and documentation of safe use conditions in order to 1) ensure that patients and prescribers make informed risk benefit decisions before and during romiplostim treatment and 2) establish the long-term safety and safe use of eltrombopag through periodic monitoring. The November 18, 2008 submission is consistent with section 505-1 "Risk Evaluation and Mitigation Strategies" of FDAAA. The eltrombopag REMS is comprised of a Medication Guide, Elements to Assure Safe Use, Implementation Plan, and timetable for assessment with the information needed for assessment.

Overall, the Promacta CARES program is consistent with the components and spirit of the Nplate NEXUS Program, approved on August 22, 2008 for the identical ITP indication. Promacta CARES Program differences are largely a result of different administration requirements (Nplate – subcutaneous weekly injection requiring HCP administration vs Promacta – oral, once daily tablet) resulting in the need for different distribution mechanisms (directly to HCP vs directly to patients). In addition, Promacta has a risk of hepatotoxicity resulting in a Boxed Warning in the product labeling. If a patient is formally discontinued due to hepatotoxicity, additional safeguards in the Promacta CARES program are designed to alert the prescriber if Promacta is restarted to ensure that the prescriber is aware of the circumstances surrounding the previous discontinuation.

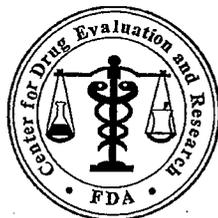
5 CONCLUSION

The REMS proposal submitted on November 18, 2008 contains components appropriately to include in a REMS. We believe that a REMS comprised of these components will appropriately evaluate and mitigate the risks of hepatotoxicity, bone marrow reticulin formation and bone marrow fibrosis, worsened thrombocytopenia after cessation of romiplostim, thromboembolic complications, increased risk of hematological malignancies, and progression of malignancy in patients with a pre-existing hematological malignancy or myelodysplastic syndrome.

APPENDICES

**APPEARS THIS WAY
ON ORIGINAL**

APPENDIX A: OSE BRIEFING DOCUMENT FOR MAY 30, 2008 ODAC



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: May 1, 2008

To: Rafel (Dwaine) Rieves, M.D., Director (Acting)
Division of Medical Imaging and Hematology Products (DMIHP)

Through: Gerald Dal Pan, M.D., M.H.S., Director
Office of Surveillance and Epidemiology (OSE)

From: OSE Risk Management Team
Suzanne Berkman, Pharm.D., Senior Risk Management Analyst (DRISK)
Mary Dempsey, Risk Management Program Coordinator (DRISK)
Claudia Karwoski, Pharm.D., Acting Director (DRISK)

Subject: Review of risk management proposal submitted April 16, 2008

Drug Name: Eltrombopag

Application Type/Number: NDA 22-291

Applicant/Sponsor: GlaxoSmithKline (GSK)

OSE RCM #: 2008-414

EXECUTIVE SUMMARY

The following review focuses on the restricted distribution and risk assessment components of the eltrombopag risk management strategy. This review does not address the proposed pharmacovigilance or proposed/ongoing pharmacoepidemiologic activities.

The Sponsor proposes a restricted distribution program with a risk assessment component primarily to ensure safe and appropriate use of eltrombopag. These components do not support the proposed short-term indication nor do they adequately address the need for additional risk assessment.

There are competing issues regarding eltrombopag and risk management. First, the controlled clinical trial experience involved relatively small numbers of patients with a short, six-week duration of exposure. The extent and significance of the available safety data are inadequate to elucidate fully the significance of certain safety concerns, leading to a need for extensive further risk assessment. Second, the proposed indication (short-term treatment) does not parallel the nature of the disease state (chronic, long-term). The need to treat ITP patients for an indefinite period of time, and the inadequacy of long-term efficacy and safety data, create a dilemma for prescribers, patients, and the development of a practical risk management approach.

The appropriateness of instituting a risk management strategy to address such major risk assessment needs versus further data analysis of longer term clinical trial data to establish safety needs to be discussed. These additional data could further focus the eventual risk management strategy or support that such measures are not necessary. The risk management strategy must support and be consistent with the approved indication and labeling which define safe and appropriate use.

1 BACKGROUND

1.1 PRODUCT INFORMATION

Eltrombopag is an oral thrombopoietin receptor agonist that interacts with the transmembrane domain of the thrombopoietin receptor, inducing the proliferation and differentiation of megakaryocytes. The signaling cascade is similar, but not identical to, that of endogenous thrombopoietin. At present, the Sponsor is proposing eltrombopag for the short-term (6 week) treatment of previously-treated adults with chronic idiopathic (autoimmune) thrombocytopenic purpura (ITP) to increase platelet counts and reduce or prevent bleeding. Eltrombopag is not recommended for use in patients who require an immediate increase (24 – 48 hours) in platelet count. A rise in platelet count can be noted within 1 to 2 weeks after initiating eltrombopag. The recommended starting dose is 50 mg by mouth once daily. If after 3 weeks, the platelet count remains less than 50,000/ μ l, the dose may be increased to 75 mg.

Because eltrombopag is orally administered once daily, it may be appealing for broader use in a variety of diseases associated with thrombocytopenia. Studies are ongoing for the use of eltrombopag for long-term treatment of ITP, treatment of thrombocytopenia secondary to cirrhosis associated with hepatitis C, and chemotherapy-induced thrombocytopenia.

1.2 SAFETY CONCERNS

The summary of the safety concerns is based on the medical officer's draft review, the Sponsor's April 16, 2008, risk management proposal, and the Sponsor's briefing document. One-hundred fifty-five ITP patients have been exposed to eltrombopag for 6 months or more with much of the data beyond 6 weeks of treatment obtained from open-label extension studies.³ Eltrombopag has risks that have been identified in clinical trials, as well as certain risks that are not yet completely characterized through animal or human study. Based on the adverse events noted in clinical trials and the biologic plausibility for certain adverse events, the following risks were identified for further risk management consideration:⁴

- **Hepatobiliary toxicity**
 - From the 120 day safety update provided by the Sponsor, across all eltrombopag studies, a total of 35 patients have experienced hepatobiliary toxicity (35/469, 7.5%) as defined by the Food and Drug Administration *Draft Guidance for Industry on the Premarketing Clinical Valuation of Drug-Induced Liver Injury*.⁵

³ Risk Management Plan (RMP) NDA No: 22291 submitted by GSK on April 16, 2008.

⁴ Data extracted from the FDA Medical Officer's [DRAFT] review of NDA 22-291 unless otherwise noted. April 30, 2008.

⁵ FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation [DRAFT]. October 2007. *This guidance provides support on the use of the following major indicators of potential severe DILI: (1) An excess of AT elevations to >3xULN compared to a control group. (2) Marked elevations of AT to 5x-, 10x-, or 20xULN in smaller numbers of subjects in the test drug group and not seen (or seen much less frequently) in the control group. (3) One or more cases of elevated bilirubin to 2xULN in a setting of pure hepatocellular injury ..., with no other*

- In the ITP studies, 16 out of 164 patients (9.7%) who received any dose of eltrombopag met the FDA criteria of hepatobiliary toxicity compared to 5/67 patients (7.5%) in the placebo group. Of the 16 eltrombopag-treated patients 3 received 30 mg, 11 received 50 mg (three increased to 75 mg in TRA 100773B) and 2 received 75 mg as a starting dose. These patients ranged in age from 19-75 years. There were 9 patients who were female and the majority were Caucasian (10 patients) followed by Asian (five patients). The Sponsor states that other than for the 1 subject who died all other hepatobiliary laboratory abnormalities resolved. The medical officer concluded that there appears to be the potential for hepatobiliary toxicity in patients treated with eltrombopag. Most of the hepatobiliary adverse events were grade 0-1 during treatment. In the 50 mg treatment group a higher percentage of grade 1 values (21%) for alkaline phosphatase was observed compared to placebo (13%). The incidence of grade 2-4 ALT elevations was 8% in the 50 mg treatment group compared to 3% in the placebo treatment group. Grade 3-4 ALT elevations were 3% and 2% in the 50 mg treatment group and placebo group respectively. The incidence of grade 2-4 AST elevations was 3% in the 50 mg treatment group compared to 2% in the placebo treatment group. Grade 3-4 AST elevations were 2% in each treatment group (50 mg eltrombopag group and placebo group). In the 50 mg treatment group a higher percentage of grade 1 values (14%) for bilirubin was observed compared to placebo (8%).⁴
- The Sponsor identified 3 possible Hy's Law⁶ cases which includes one patient who died. The Sponsor states that 2 of the cases were confounded and 1 involved indirect hyperbilirubinemia.

It is important to note that a typical new drug application usually will not show any cases of severe drug-induced liver disease (DILI), even for a drug that can cause liver injury. The *Draft Guidance for Industry Drug Induced Liver Injury: Premarketing Clinical Evaluation* further states, in pertinent part:

Only the most overt hepatotoxins can be expected to show cases of severe DILI in the 1,000 to 3,000 subjects typically studied and described in a new drug application (NDA). ... Most of the drugs withdrawn from the market for hepatotoxicity have had rates of death or transplantation in the range of ≤ 1 per 10,000, so that a single case of such an event would not be reliably found even if several thousand subjects were studied. Cases of severe DILI have rarely been seen in drug development programs of significantly hepatotoxic drugs. ... Finding one Hy's Law⁶ case in clinical trials is ominous; finding

explanation ... accompanied by an overall increased rate of AT elevations >3xULN in the test drug group compared to placebo. The draft guidance further states that assessment of rates should include:

- 3x-, 5x-, 10x-, and 20xULN elevations of AST, ALT, and either ALT or AST.
- Any elevations of bilirubin; elevated bilirubin to >1.5xULN, and to >2xULN.
- Any elevations of ALP >1.5xULN
- Elevation of AT (>3xULN) accompanied by elevated bilirubin (>1.5xULN, >2xULN).
- Possibly liver-related deaths and liver-related treatment discontinuations.

⁶ FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation [DRAFT]. October 2007. Hy's law cases have the following components - 1. The drug causes hepatocellular injury, generally shown by more frequent 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control agent or placebo. 2. Among subjects showing such AT elevations, often with ATs much greater than 3xULN, some subjects also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (serum alkaline phosphatase (ALP) activity >2xULN). 3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury.

two is highly predictive of a potential severe DILI. It is critical, however, to determine whether mild hepatotoxicity reflects a potential severe DILI or reflects a capacity for only limited injury.

- **Post-therapy decrease in platelet count**

- In the two studies supporting this application (TRA 100773A and TRA 100773B), there appears to be a trend for transient thrombocytopenia observed within 4 weeks of discontinuation of eltrombopag therapy.
- In study TRA 100773A, 6 patients out of 117 (1 placebo, none in the 30 mg eltrombopag group, 3 in the 50 mg eltrombopag group, and 2 in the 75 mg eltrombopag group) had platelet counts $< 10,000/\mu\text{l}$ and a decrease in platelet count on at least one occasion $< 10,000/\mu\text{l}$ compared to baseline within 4 weeks after discontinuation of study medication. All 5 patients who received eltrombopag were defined as responders. Three patients achieved platelet counts $\geq 200,000/\mu\text{l}$. The WHO bleeding score increased from baseline in 3 patients and these 3 patients received rescue medication.
- In study TRA 100773B, 11 patients out of 114 (8 patients treated with eltrombopag and 3 patients treated with placebo) had platelet counts $< 10,000/\mu\text{l}$ and at least $10,000/\mu\text{l}$ less than baseline platelet count within four weeks after discontinuation of study medication. The bleeding score increased in 3 patients.

- **Thrombotic/thromboembolic events**

- In study TRA 100773A, 1 patient had a serious adverse event of pulmonary embolism and thromboemboli. No other thromboembolic events were reported in any other study patient during the treatment or post-therapy phases of this study. Of the 12 patients who achieved a platelet count $> 400,000/\mu\text{l}$ during treatment, 2 patients (both in the 50 mg treatment group) received medication for prophylaxis of thrombosis in response to their increase in platelets. These 2 patients achieved platelet counts of $555,000/\mu\text{l}$ and $625,000/\mu\text{l}$ at day 15. They were discontinued from study medication and received aspirin therapy along with antacid therapy for 3 days. No adverse events were reported in either patient.
- In study TRA 100773B, there were no thromboembolic adverse events reported in either treatment group.
- Thromboembolic events were reported in the open-label extension studies; however, the current review is focused on short-term use.

- **Bone marrow reticulin formation/marrow fibrosis**

- There is concern that the risk of marrow fibrosis could be associated with eltrombopag but the data are limited to support or refute these risks.
- Data from rats, monkeys, and mice reflect no efficacy so other hematopoietic effects may be blunted or may not occur in these species. Therefore, the absence of hematopoietic toxicity in these species may not reflect an absence of risk.
- The ITP studies submitted to support this application (TRA 100773A and TRA 100773B) did not evaluate the bone marrow for toxicity in patients treated with eltrombopag.
- In the 120-day safety update, the Sponsor reported that 19 patients who were treated for at least 13 months with eltrombopag in the one of the open-label extension trials had

bone marrow biopsies. The Sponsor states that reticulin/collagen was reported in 9 of the 19 bone marrow biopsy reports and that 2 of 9 had grade 2 reticulin deposition.

It is not completely understood if short-term, long-term or repeated cycle treatment of ITP with eltrombopag may increase the risk of myelofibrosis. While the specific mechanism of action on a cellular level may differ slightly from romiplostim, there is still a theoretical concern regarding the risk of reticulin formation leading to marrow fibrosis. In the absence of substantive data supporting a lack of these risks, it seems prudent to suspect a possible class effect at this time.

- **Malignancy progression**

- There is concern that the risk of malignancy progression could be associated with eltrombopag but the data are limited to support or refute these risks. Presently, there is an ongoing trial evaluating the use of eltrombopag to treat chemotherapy-induced thrombocytopenia in patients with advanced solid tumors.
- Data from rats, monkeys, and mice reflect no efficacy, so other hematopoietic effects may be blunted or may not occur in these species. Therefore, the absence of hematopoietic toxicity in these species may not reflect an absence of risk. While the specific mechanism of action on a cellular level may differ slightly from romiplostim, there is still a theoretical concern regarding the risk of malignancy progression. In the absence of substantive data supporting a lack of these risks, it seems prudent to suspect a possible class effect at this time.

- **Cataracts**

- Treatment-related cataracts were observed in mice given 75 or 150 mg/kg/day and rats given 40 mg/kg/day. In these rodents, the ocular changes were observed after seven weeks of treatment.
- In study TRA 100773B, 49 of 117 patients had ocular assessments in the safety population. In these 49 patients there were 14 reports of cataracts. Three patients had a cataract observed at baseline and none of these patients had cataract progression over the course of the study. There were 10 patients who had cataract observed at the time of the first ocular examination and 1 patient was observed to have a cataract formation after the first ocular examination.
- In study TRA 100773B, 112 of 114 patients in the safety population had ocular assessments for cataracts. Cataracts were observed at baseline in 9 patients of which 3 patients had progression of their cataracts. There were 101 patients who had no evidence other cataract observed at baseline. Of these 101 patients, 4 patients subsequently developed cataracts.

- **Phototoxicity**

- An *in vitro* phototoxicity study was conducted and eltrombopag was observed to be toxic in the presence of ultraviolet illumination.
- In the ITP studies submitted to support this application (TRA 100773A and TRA 100773B), there was 1 report of photosensitivity in an eltrombopag treated patient which was characterized as a grade 2 adverse event.

- **Renal tubular toxicity**

- A 2-year carcinogenicity study in mice showed dose-related renal tubular toxicity.

- The Sponsor states that in the intermittent or long-term studies, renal-related adverse were generally mild to moderate (grade 1 or 2) and none led to withdrawal from study medication.

The proposed restricted distribution program and post marketing risk assessment component do not address the risk for cataract and phototoxicity or the potential risk of renal tubular toxicity.

2 RISK MANAGEMETN OF ELTROMBOPAG

2.1 LABELING

The Sponsor proposes to include the risk of hepatotoxicity in the Warnings and Precautions section of the label (package insert) along with a recommendation to monitor "hepatobiliary laboratory values" every 2 weeks for the first 3 months of treatment and monthly thereafter. This recommendation assumes treatment beyond a 6 week course. The Sponsor also proposes to develop discontinuation criteria for use when hepatobiliary adverse reactions occur. The label will include Warnings and Precautions on photosensitivity, thromboembolism, and post-discontinuation thrombocytopenia.

Based on the risk management proposal submitted on April 16, 2008, the Sponsor does not plan to address the risk of malignancy, reticulin formation, renal tubular toxicity, or cataract in the proposed label (package insert). We note other submissions from the Sponsor include the risks of renal tubular toxicity and cataract in the proposed label.

The Sponsor proposes a patient information leaflet.

2.2 SUMMARY OF SPONSOR'S PROPOSED RISK MANAGEMENT PROPOSAL

The risk management proposal submitted April 16, 2008, was reviewed. The Sponsor states that the program goals are to:

- ensure the safe and appropriate use of eltrombopag,
- promote informed risk-benefit decisions regarding the use of eltrombopag,
- determine the incidence and risk factors for the identified and potential risk of eltrombopag use, and to
- further assess the overall safety profile of eltrombopag.

The objectives are to:

- enroll all patients and prescribers,
- assure that patients and prescribers make informed risk-benefit decisions regarding the use of eltrombopag,
- provide long-term monitoring and active pharmacovigilance of all patients receiving eltrombopag,
- provide quantitative data on the incidence and risk factors for the identified and potential risks of eltrombopag, and to
- monitor and assess off-label use.

The Sponsor proposes to meet these goals and objectives through labeling, additional educational efforts, and a restricted distribution program that requires patient and healthcare provider

enrollment through the completion of a prescriber/patient agreement in order to prescribe and receive eltrombopag. In addition, prescribers will be required to complete a safety questionnaire every 6 months for the first two years of treatment for each patient. While the Sponsor anticipates that the majority of eltrombopag will be distributed through registered specialty pharmacies, a plan to develop a mechanism for hospital pharmacies and oncology clinics to register, acquire, and dispense eltrombopag is ongoing. The Sponsor will contract with a third party to manage the entire program, which will be operational at the time of product launch.

None of the program materials have been provided.

In addition to the strategies outlined above, the Sponsor states that no direct-to-consumer media (television or radio) will be used. It is unclear if print advertisements will be utilized.

Education

- *Healthcare Providers*

The Sponsor proposes that the approved labeling (package insert) will serve as the primary piece for healthcare provider education. We note that it will be difficult to use the label as the sole means to educate healthcare providers on all the risks identified by the Sponsor for risk management if not all of those risks are included in labeling (i.e., malignancy, reticulín formation, renal toxicity, and cataract). Educational materials must be consistent with the approved labeling.

The proposal does not include mention of any materials educating healthcare providers on the elements of the program, including the need to enroll patients, the frequency of required laboratory monitoring (if any), and the requirement to complete follow-up questionnaires.

The Sponsor proposes other routine efforts such as detailing and medical liaison support. However, in absence of the actual materials, it is difficult to determine if these efforts will truly serve an educational purpose or function primarily to promote and market eltrombopag.

- *Patients*

The Sponsor states that the patient information leaflet will serve as the primary piece for the prescriber to review with the patient prior to treatment initiation. We note it will be difficult to use the patient information leaflet as the primary means to educate patients on all the risks identified by the Sponsor for risk management if not all of those risks are included in labeling (i.e., malignancy, reticulín formation, renal toxicity, and cataract).

Additional materials such as a patient education booklet and a starter kit (containing the patient education booklet and a patient diary to record platelet counts) will also be created. It will be difficult to develop educational materials that include risks that are not discussed in the approved labeling. The Sponsor also states that booklet will be distributed to patients whether or not they are enrolled in the "compliance program" and that patients can "opt in" to the "compliance program." Further, patients who enroll in the "compliance program" will receive a phone call from a trained nurse upon enrollment and be provided with specific information about compliance and safety issues. It is unclear what the "compliance program" is and how it differs from the restricted distribution and risk assessment program.

Elements to Assure Safe Use

The proposal states that all prescribers, dispensing entities, and patients will need to be authorized in order to prescribe, dispense, and be treated with eltrombopag, respectively. The following provides an overview of the various components and highlights areas requiring additional clarity/refinement.

- *Prescriber/Patient Components*

Prescribers and patients will enroll simultaneously by completing a patient-physician agreement form. This form verifies that the prescriber will (in pertinent part):

- enroll all patients in the program,
- review the key benefits and risks of eltrombopag with the patient,
- complete follow-up questionnaires for each patient every 6 months for 2 years,
- report any adverse events during eltrombopag treatment to GSK, and
- provide the diagnosis for treatment with eltrombopag.

The patient attests that he/she understands the risks and benefits associated with eltrombopag.

- *Pharmacy Components*

Eltrombopag will be available only through authorized pharmacies and dispensing clinics and will not be available through non-institutional retail pharmacies. Authorized dispensing entities will agree to (in pertinent part):

- only dispense eltrombopag to patients enrolled in the program,
- distribute the patient information leaflet each prescription dispensed, and
- only dispense a 42-day supply at a time.

Specialty pharmacies will ship eltrombopag directly to the patient. It is not clear how local dispensing entities will authorize/track each prescription dispensed to assure safe use conditions.

- *Safe Use Condition Components*

The program will utilize the following components to assure safe use:

- Prescribers and patients must be enrolled in the program in order for the patient to receive eltrombopag.

Comments

- *The proposal does not include any condition for re-authorization or prompt to evaluate the appropriateness of continuing treatment beyond 6 weeks.*
- *It is not clear how the program will document if the patient should not receive eltrombopag. For example, if the patient experiences a serious adverse event that requires drug discontinuation, how will the program assure that the patient is not inappropriately re-challenged?*

- Only authorized pharmacies will be able to dispense eltrombopag to patients enrolled in the program.

Comment

- *The proposal does not explain how local dispensing entities (i.e., hospitals, oncology clinics) will authorize/track each prescription dispensed to assure safe use conditions.*

- Prescribers must complete a safety questionnaire every 6 months for the first two years of treatment. The questionnaire will focus on hepatobiliary abnormalities, thromboembolic events, increased bone marrow reticulin, and malignancies.

Comments

- *It is not clear how the program will ensure that the safety questionnaire is completed as it does not appear to be linked to product access.*
- *It is not clear what depth of data collection will be gleaned from this questionnaire. Further, this form does not appear to capture post-discontinuation decreases in platelet count.*
- *The rationale for data collection limited to the first two years is not clear.*
- Prescriptions for eltrombopag will be limited to a 42-day supply.

Comment

- *The proposal does not include limiting refills, creating a treatment stop date, or creating a time requirement between re-initiation of treatment despite the fact that the current indication is for short-term (6 week) treatment. Therefore, the benefit and utility of a 42-day supply to assure safe use is not clear.*
- The patient information leaflet will be dispensed with each prescription.

Comment

- *Considering that the drug product is one for which patient labeling could help prevent serious adverse effects and that it has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients decision to use or continue to use the product, a Medication Guide could be considered for eltrombopag.⁷*

Program Evaluation

The Sponsor proposes to report semiannually on the overall program for the first two years after launch. The Sponsor states that the report will focus on assessing the effectiveness of the elements utilized in the program. This will be accomplished by evaluating compliance with program objectives (outlined above). Two of the objectives are to “provide long-term monitoring and active pharmacovigilance of all patients” and “provide quantitative data on the incidence and risk factors for the identified and potential risks of eltrombopag.” However, the proposed program evaluation focuses more on program compliance (“quantify the estimated percentage of physicians and patients receiving commercial PROMACTA” and “collection of safety questionnaires” by the third party) rather than safety data assessment.

The Sponsor also states that surveys will be developed to assess prescriber and patient “knowledge of key benefits and risks” of eltrombopag. No further information about the frequency, content, or implementation plan for these surveys is provided.

2.3 KEY COMMENTS ON SPONSOR PROPOSAL

The Sponsor propose restricted distribution and risk assessment to assure safe and appropriate use of eltrombopag and further assess risk. While we agree with the program goals, certain components of the plan are not explained or absent. These issues need to be addressed to better assure appropriate use and adequate risk assessment.

The Sponsor submitted a new drug application to support the use of eltrombopag for the short-term treatment of chronic ITP. Based on the duration of use in the controlled clinical trials,

⁷ 21 CFR 208.1(c).

“short-term” translates to 6 weeks of daily eltrombopag treatment. At present, the proposed program fails to include any measures to limit use to short-term (6 weeks) treatment or to prompt evaluation of the appropriateness of continuing therapy beyond 6 weeks. In fact, the proposal diminishes any significance to the duration of use by proposing a safety evaluation every 6 months. This misleadingly implies that use beyond 6 weeks is safe and effective (this indication has not yet been submitted to the Agency for consideration). Therefore, the proposed safety assessment every 6 months is not consistent with the proposed indication and label (package insert) which serves to define appropriate use.

The need for further risk characterization for eltrombopag is evident considering:

- the limited number of patients exposed over a short period of time in the controlled clinical development program,
- the safety concerns identified in animal data (renal toxicity, cataracts, and phototoxicity) and/or the biologic plausibility for other certain significant adverse events (reticulin formation/myelofibrosis, malignancy),
- the safety concerns not identified in animal data possibly because of the lack of hematopoietic effect in the species tested (rats, monkeys, mice),
- the need for options to treat thrombocytopenia associated with various diseases, and
- the potential appeal of a once daily tablet to increase platelet count.

These factors contribute to the concern regarding long-term and/or off-label use. They place burden on the program to not only attempt to mitigate risk but to support major risk assessment associated with long-term treatment in effort to enhance patient safety. The proposed program includes no baseline data collection component beyond the patient’s diagnosis in order to establish and monitor who is being treated with eltrombopag. There is no mention to monitor hepatobiliary function. There is no mention of program/treatment discontinuation procedures. These procedures would attempt to mitigate and assess post-discontinuation thrombocytopenia as well as to establish data on the reasons for discontinuation (which may be related to an adverse event). The program lacks any link to assure short term-use or to direct appropriate longer term safe use conditions. The proposal includes no reauthorization component at the 6 week post-initiation time point or at any time point. It is unclear how the program will ensure that the safety questionnaire is completed. While addressing these issues will further expand the program, it is important to create a program that will elicit valuable, relevant information about eltrombopag. The need for further risk assessment with long-term use is a major driver for establishing this sort of program. If the program is not adequately designed to collect substantive data to further inform safe, appropriate use of eltrombopag, it becomes more an exercise in bureaucracy than risk management.

3 DISCUSSION

There are a number of issues to consider with eltrombopag involving its proposed indication, current safety profile, and the appropriateness of risk management under the current circumstances. The data appear to support eltrombopag for short-term use. The proposed indication is consistent with these data. Therefore at present, “appropriate use” of eltrombopag is limited to a 6 week course. However, practically thinking, the nature of the disease (chronic, long-term thrombocytopenia) and anticipated actual use of eltrombopag is not consistent with this scenario. Further, decreases in platelet count below pre-treatment levels have been identified as a known risk upon eltrombopag discontinuation. Therefore, designing the risk management program to assure appropriate use (i.e., compliance with a 6 week treatment course), may spur adverse events. However, if a program cannot be developed to support the indication, it calls into

question whether a short-term treatment indication is viable. If the data cannot support long-term use and it does not make sense to limit treatment to short-term use, the proposed program will be almost entirely a means for further data collection with little effort toward risk mitigation. This raises the question whether eltrombopag needs additional clinical study or a risk management program.

While a risk management program is a path for further risk assessment, it is not meant to be a substitute for, or a means to circumvent, sufficient study through controlled clinical trials. Weighing whether eltrombopag provides a meaningful therapeutic benefit based on the current proposed indication and whether a risk management program can ensure that the benefits outweigh the risks based on what is currently known about the product is prudent. Moreover, the label should reflect the risks identified for further risk management. Risk management plans are targeted to manage significant risks. If these risks are not characterized enough to be included in a label but significant concerns exist that warrant additional risk management activities, this further raises the question as to the need for further study prior to approval.

4 CONCLUSION

Because the clinical trial experience involved relatively small numbers of patients and limited duration of exposure, the extent and significance of the available safety data are inadequate to elucidate fully the significance of certain safety concerns. Further, the nature of the disease can require the need for long-term treatment while the data and proposed indication support short-term use. The appropriateness of instituting a risk management strategy versus further data analysis of longer term clinical trial data to establish safety and efficacy should be discussed. These additional data could further focus the eventual risk management strategy or provide support that such measures are not necessary.

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Draft Labeling (b4)

Draft Labeling (b5)

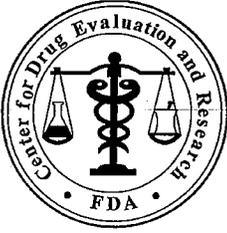
Deliberative Process (b5)

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: September 10, 2008

To: Rafel D. Rieves, M.D., Acting Director
Division of Medical Imaging and Hematology Products

Through: Jodi Duckhorn, M.A., Team Leader
**Patient Labeling and Education Team
Division of Risk Management (DRISK)**

From: Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Specialist
**Patient Labeling and Education Team
Division of Risk Management (DRISK)**

Subject: Review of Patient Labeling (Medication Guide)

Drug Name(s): Promacta (eltrombopag) Tablets

Application Type/Number: NDA 22-291

Applicant/sponsor: GlaxoSmithKline

OSE RCM #: 2008-774

1 INTRODUCTION

GlaxoSmithKline submitted an original New Drug Application, NDA 22-291 for Promacta (eltrombopag olamine) Tablets on December 18, 2007. Promacta is indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. The sponsor submitted labeling in the form of Professional Information on December 18, 2007 and further revised the labeling on May 9, 2008, and on June 26, 2008.

The review division advised the sponsor that a Risk Evaluation and Mitigation Plan (REMS) will be required for Promacta. The sponsor submitted their proposed REMS on August 5, 2008, with the exception of the proposed Medication Guide, which was converted from a proposed Patient Package Insert, and submitted on August 8, 2008. The review division and the sponsor met on August 8, 2008 to discuss the proposed REMS.

The REMS has been addressed in a separate review by DRISK. This review is written in response to a request from the review division to review the sponsor's proposed Medication Guide. The review division revised the MG submitted by the sponsor to be consistent with the approved Nplate (romiplostim) Medication Guide to the extent that the safety issues are similar.

2 MATERIAL REVIEWED

- DRAFT Promacta (eltrombopag olamine) Tablets Professional Information submitted by the sponsor and further revised by the review division on September 5, 2008 and September 8, 2008.
- DRAFT Promacta (eltrombopag olamine) Tablets Medication Guide submitted by the sponsor on August 8, 2008 and further revised by the review division on August 29, 2008.
- DDMAC Review of the sponsor's proposed Promacta (eltrombopag olamine) Tablets Medication Guide, dated August 28, 2008.

3 DISCUSSION

The purpose of Medication Guides (MG) is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft MG submitted by the sponsor has a Flesch Kinkaid grade level of 8.7, and a Flesch Reading Ease score of 55.9%. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). Our revised MG has a Flesch Kinkaid grade level of 8.3 and a Flesch Reading Ease score of 59.4%.

In our review of the MG, we have:

- simplified wording and clarified concepts where possible,
- made the MG consistent with the PI,
- rearranged information due to conversion of the PI to PLR format,
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

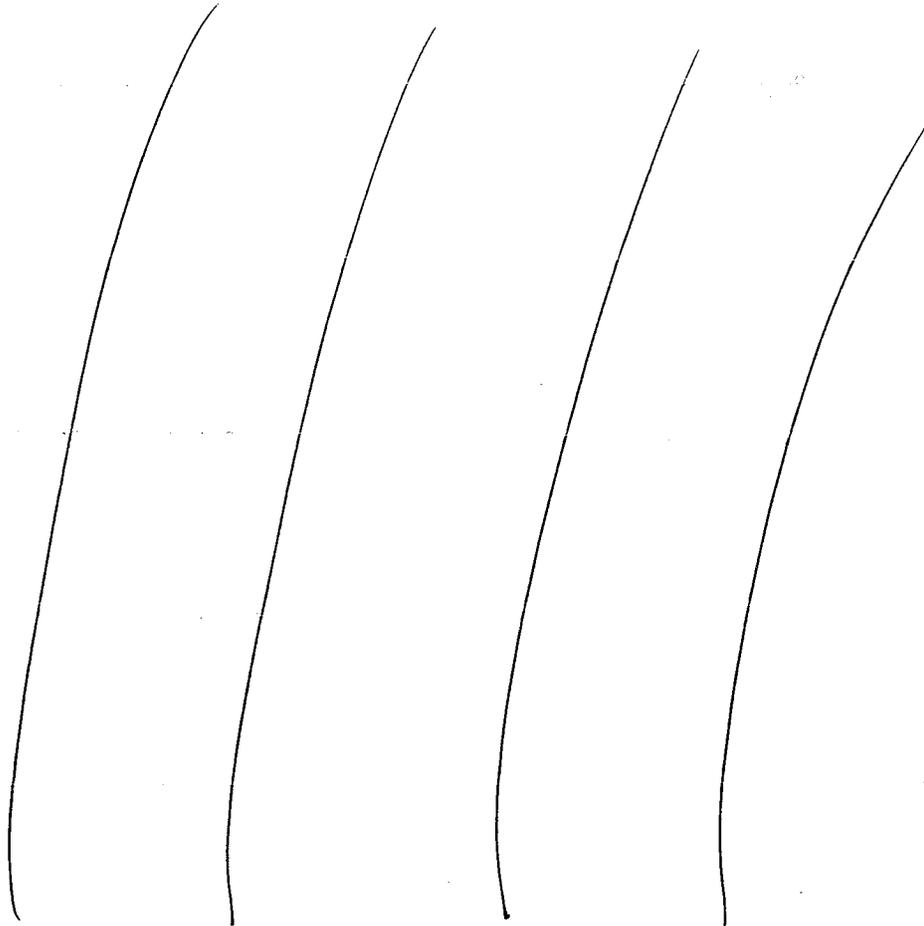
In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APFont to make medical information more accessible for patients with low vision. We have reformatted the MG document using the font APFont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are **bolded, underlined and italicized**.

We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

4 CONCLUSIONS AND RECOMMENDATIONS



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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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