Initial REMS Approval: 11/2008
Most Recent Modification: 12/2011

NDA 22-291

PROMACTA® (eltrombopag)

GlaxoSmithKline

Upper Providence, 1250 South Collegeville Road, Collegeville, PA, 19426, USA

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

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

II. REMS ELEMENTS

A. Communication Plan

GlaxoSmithKline will implement a communication plan to healthcare providers to support implementation of this REMS.

The communication plan will provide for the dissemination of information about the elimination of the elements to assure safe use, inform prescribers and pharmacists how to obtain PROMACTA tablets, and remind healthcare providers about the serious risks associated with PROMACTA tablets and appropriate patient selection in accordance with the approved labeling.

The communication plan will include:

1. A *Dear Healthcare Provider Letter* will be distributed via direct mail, electronic delivery or via a hand carry program to the following within 15 working days of the most recent REMS approval 12/2011:
    - Hematologists
    - Oncologists
    - Pharmacies

In addition, GlaxoSmithKline will send the *Dear Healthcare Provider Letter* to MedWatch at the same time it is disseminated to the target audience.

The *Dear Healthcare Provider Letter* is part of the PROMACTA REMS and is appended.

2. A *Dear Professional Society Letter* that will be distributed to the leadership of the following societies via direct mail or electronic delivery within 15 working days of the most recent REMS approval 12/2011:
    - American Society of Clinical Oncology (ASCO)
    - American Society of Hematology (ASH)
    - Oncology Nursing Society (ONS)
    - National Comprehensive Cancer Network (NCCN)
    - Hematology Oncology Pharmacy Association (HOPA)
    - American Society of Pediatric Hematology/Oncology (ASPHO)
    - American Society of Health-System Pharmacists (ASHP)

The *Dear Professional Society Letter* is part of the PROMACTA REMS and is appended.

Both letters will be posted on www.promactacares.com within 5 working days of the most recent REMS approval 12/2011. This information will remain on the website for 6 months.

III. Timetable for Submission of Assessments

GlaxoSmithKline will submit REMS Assessments to the Food and Drug Administration (FDA) on June 30, 2012, June 30, 2015, and June 30, 2019 for the PROMACTA (eltrombopag) REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. GlaxoSmithKline will submit each assessment so that it will be received by the FDA on or before the due date.

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www.gsk.com

IMPORTANT PRESCRIBING INFORMATION

Date: *To be inserted locally*

Subject:
- **PROMACTA REMS Program: Elimination of Prescriber, Pharmacy, and Patient Enrollment requirements to prescribe, dispense and receive PROMACTA**
- **Serious risks associated with PROMACTA**

Dear Healthcare Professional:

As of <*insert date of program closure (Day 0)*>:

- **Healthcare Professionals/Prescribers** – No longer need to be enrolled to prescribe PROMACTA or complete and submit safety forms
- **Pharmacies** - No longer need to enroll. Pharmacists no longer need to verify prescriber and patient enrollment before dispensing PROMACTA
- **Patients** - No longer need to be enrolled in order to receive PROMACTA

Any prescriber or hospital will be able to order PROMACTA without enrolling either themselves or patients.

Why are the REMS restricted distribution requirements being eliminated?

The restrictive elements of the REMS included enrollment of prescribers, patients, and pharmacies to assist in collecting long term safety information. Upon further review, FDA and GSK have determined that the safety information collected through the REMS, which is based on individual case safety reports, is inherently confounded by underlying medical conditions in the treated population and thus cannot be used to determine the precise role of PROMACTA in the development of the adverse events. Based in part on this determination and the data submitted from clinical trials, FDA and GSK have concluded that the restrictive elements of the REMS can be eliminated. For this reason, enrollment of prescribers, patients, and pharmacies, and mandatory collection of safety data is no longer required.

What has changed?

Prescribers

- No longer need to enroll in PROMACTA CARES
- No longer need to enroll patients in PROMACTA CARES
- No longer need to complete and submit the enrollment, baseline, medical and reauthorization, and discontinuation and post-therapy forms

Prescribers should inform their patients previously or currently enrolled in PROMACTA CARES of the elimination of this program.

Pharmacists

- No longer need to complete initial pharmacy enrollment forms and training
- No longer need to confirm prescriber and patient enrollment in PROMACTA CARES with each prescription/refill

- No longer need to maintain and submit a record verification Inventory Tracking Log
- No longer need to undergo periodic audits to ensure PROMACTA is dispensed in accordance with program requirements

Ordering PROMACTA

- There are no restrictions on ordering PROMACTA
- **There is no change to the ordering process for PROMACTA.** PROMACTA will continue to be available through specialty pharmacies, hospital pharmacies and dispensing clinics. GSK will continue to offer the patient assistance programs and reimbursement support programs through CARES by GSK (www.CARESbyGSK.com)

What has NOT changed?

Risks

PROMACTA is associated with serious risks including:

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

- *Reticulin fiber deposition*: PROMACTA may increase the risk for development or progression of reticulin fiber deposition within the bone marrow. Monitor peripheral blood for signs of marrow fibrosis.
- *Thrombosis/Thromboembolism* may result from increases in platelet counts with PROMACTA. Portal vein thrombosis has been reported in patients with chronic liver disease receiving PROMACTA.
- *Hematologic Malignancies*: PROMACTA may increase the risk for hematologic malignancies. 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.

Indication

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.

- 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 to an attempt to normalize platelet counts.

Please see Prescribing Information for complete description of safety information, including BOXED WARNING

Prescribers

- Continue to discuss the benefits and risks of PROMACTA with your patients
- Select the appropriate patients to receive PROMACTA in accordance with the approved prescribing information
- Monitor your patients as specified in the Prescribing Information
- Continue to report adverse drug reactions to GSK

Pharmacists

- Continue to provide the Medication Guide with each prescription/refill.
- Continue to report adverse drug reactions to GSK.

What about records I collected for the PROMACTA CARES Program?

Enrolled prescribers and pharmacies should maintain patient and PROMACTA CARES Program records in accordance with state and local records retention requirements.

What if I have safety information to submit?

- GSK will continue to accept safety information for enrolled patients for an additional 4 weeks, safety information can be faxed to 866-765-0920 or provided by phone at call 1-877-977-6622
- After <<*insert date*>>, report SUSPECTED ADVERSE REACTIONS, to GSK Inc. at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

GSK will not send any additional reminders to prompt safety data collection. This letter serves as the final request for information.

What will GSK do with the patient health information already collected?

Patient health information and data collected throughout the PROMACTA Cares program continues to be protected and will be disclosed only for the purposes described in the patient enrollment form.

Further Information

Should you require additional information about PROMACTA please refer to the Prescribing Information found at http://us.gsk.com/products/assets/us_PROMACTA.pdf or contact GSK Customer Response Center at 1-888-825-5249.

Sincerely,

Manuel Aivado, MD
Director, Global Clinical Development Oncology
GlaxoSmithKline

References

Prescribing Information for PROMACTA <<*month*>>, 2011.

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References

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

/s/

ROBERT C KANE
12/06/2011