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NDA 22-291 PROMACTA® (eltrombopag)

GlaxoSmithKline

PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

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

II. REMS ELEMENTS

A. 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. Please see the appended Medication Guide.

B. Elements To Assure Safe Use

1. 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* at 1-877-9-PROMACTA (or 1-877-977-6622). The

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prescriber must receive the Prescriber Enrollment Confirmation Letter, via fax to confirm the prescriber's enrollment into PROMACTA *CARES*. To enroll, the Prescriber must attest to the following:

- I have read the full Prescribing Information for PROMACTA.
- I understand that PROMACTA is 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.
- I understand that PROMACTA is only indicated for use in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk of bleeding.
- I understand that PROMACTA should not be used in an attempt to normalize platelet counts.
- I understand that PROMACTA is not indicated for the treatment of thrombocytopenia due to causes of thrombocytopenia (e.g., myelodysplasia or chemotherapy) other than chronic ITP
- I understand the following risks are associated with PROMACTA:
    - PROMACTA administration may cause hepatotoxicity. If a patient develops serious liver function test abnormalities, I should discontinue treatment with PROMACTA.
    - PROMACTA increases the risk for development or progression of reticulin fibers within the bone marrow. If the patient develops new or worsening morphological abnormalities or cytopenia(s), I should discontinue treatment with PROMACTA and consider a bone marrow biopsy, including staining for fibrosis.
    - Discontinuation of PROMACTA may result in thrombocytopenia of greater severity than was present prior to therapy with PROMACTA. Serious hemorrhagic events requiring the use of supportive ITP medications occurred in clinical studies within one month following the discontinuation of PROMACTA.
    - Thrombotic/thromboembolic complications may result from excessive increases in platelet counts.
    - Stimulation by PROMACTA of the TPO receptor on the surface of hematopoietic cells may increase the risk for hematologic malignancies, especially in patients with myelodysplastic syndrome.

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- I understand that each patient should be monitored as follows to assure safe use of PROMACTA:

  Complete Blood Count:

  - Monitor CBCs, including platelet counts and peripheral blood smears, prior to initiation, and weekly during the dose adjustment phase of therapy with PROMACTA.
  - Monitor CBC, including platelet counts and peripheral blood smears, monthly following establishment of a stable dose of PROMACTA.
  - If PROMACTA is discontinued, obtain CBCs, including platelet counts weekly for at least 4 weeks after discontinuation.

  Liver Tests:

  - Monitor serum liver tests (ALT, AST, bilirubin) prior to initiation of PROMACTA.
  - Monitor serum liver tests (ALT, AST, bilirubin) every 2 weeks during the dose adjustment phase and then monthly following establishment of a stable dose of PROMACTA.
  - If abnormal levels are detected, monitor serum liver tests within 3 to 5 days, then 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 of hepatic decompensation.

- Reinitiating treatment with PROMACTA after discontinuation due to hepatotoxicity is not recommended and should be considered only with close medical supervision and under exceptional circumstances where the potential benefit outweighs the risk. If liver test abnormalities persist, worsen or recur, then permanently discontinue PROMACTA.

- I understand that I am required to complete this Prescriber Enrollment Form to enroll (once) myself in PROMACTA *CARES*.

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- I will enroll each patient by assisting in the completion of the PROMACTA *CARES* Patient Enrollment Form and completing the PROMACTA *CARES* Patient Baseline Form at the time of enrollment or within 30 days of patient enrollment. I understand that baseline data is only to be used to assess for risk factors for adverse events and to evaluate the long-term safety of PROMACTA. I will obtain the patient's signature on the Patient Enrollment Form, place the original signed form in the patient's medical record, send a copy to PROMACTA *CARES*, and give a copy to the patient.

- I will provide each patient with the Medication Guide for PROMACTA prior to providing each prescription and counsel each patient on the risks and benefits of PROMACTA.

- I will evaluate the patient's status every 6 months to determine whether the patient should continue PROMACTA, and if so, authorize treatment for another 6 months

- I will notify PROMACTA *CARES* when a patient discontinues PROMACTA by completing the Patient Discontinuation and Post-Therapy Follow-up Form for PROMACTA *CARES* at the time of discontinuation of PROMACTA and complete the same again 3 months later.

- I will promptly report to PROMACTA *CARES* any adverse event occurring in the course of the use of the drug as described in the Medical and Reauthorization Form for PROMACTA *CARES.*

- I understand that it is my responsibility to ensure appropriate transition of patients to the outpatient setting if my patient(s) is initiated on PROMACTA as an inpatient.

- I understand GlaxoSmithKline (GSK), its agents, and contractors may contact me via phone, mail, or e-mail to assess the effectiveness of the program requirements for PROMACTA *CARES.*

- I understand if I fail to comply with the requirements of PROMACTA *CARES*, I may no longer be able to participate in PROMACTA *CARES.*

- I further understand that I have sole responsibility for all medical judgments and treatments, and have sole responsibility, prior to administration of PROMACTA, to counsel each patient on the risks of PROMACTA, and provide each patient with all necessary warnings concerning PROMACTA.

GSK must maintain a database of all certified prescribers in the PROMACTA *CARES* Program. GSK must monitor to ensure that only certified prescribers are prescribing PROMACTA.

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GSK must monitor practitioner compliance with the certification program, including baseline data collection, the periodic safety monitoring and reauthorization, discontinuation procedure, and post-discontinuation follow-up of all patients treated with PROMACTA. If a practitioner is found to be non-compliant with the PROMACTA *CARES* Program, GSK must prevent the practitioner from prescribing PROMACTA.

Please see the following appended materials:

- 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.PROMACTA*CARES*.com)

2. 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. Please refer to the appended Controlled Distribution procedure.

- 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* at 1-877-9-PROMACTA (or 1-877-977-6622)**.** 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 the following:

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- I understand that PROMACTA is only available through PROMACTA *CARES*. I understand that only prescribers enrolled in PROMACTA *CARES* can prescribe PROMACTA and only patients enrolled in PROMACTA *CARES* can be dispensed PROMACTA.
- I will train and provide educational materials to appropriate staff responsible for dispensing PROMACTA. The materials will address the safe and appropriate use of PROMACTA, program monitoring requirements, program adverse event reporting requirements and documentation requirements.
- I will confirm the prescriber and patient are enrolled in PROMACTA *CARES* with each prescription/refill.
- I will verify whether the patient is authorized to receive PROMACTA prior to dispensing each prescription/refill by calling 1-877-977-6622 to receive the unique prescription verification number. I will record the verification number on the Inventory Tracking Log. If a prescription verification number is not provided, PROMACTA cannot be dispensed.
- I will provide a Medication Guide each time I dispense PROMACTA.
- I will maintain and complete the Inventory Tracking Log for every prescription/refill dispensed.
- I understand that each pharmacy site is required to submit the completed Inventory Tracking Log within 10 days of the last day of each month to PROMACTA *CARES*. I will retain a copy of the Inventory Tracking Log for at least 2 years from the date of the final log entry.
- I will cooperate with periodic audits to assure that PROMACTA is dispensed in accordance with the program requirements.

Please see the following appended materials:

- 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.PROMACTA*CARES*.com)

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

The patient with the assistance of the prescriber (or healthcare provider on his/her behalf) must complete the Patient Enrollment Form and the prescriber must fax the form to PROMACTA *CARES* at 1-877-9-PROMACTA (or 1-877-977-6622). 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. Patient enrollment requires the patient to attest to the following:

- I have read and understand the Medication Guide for PROMACTA that my prescriber has given to me.
- I have asked and discussed any questions or concerns about PROMACTA or my treatment with my healthcare provider.
- I am aware that PROMACTA is associated with the following risks:
    - PROMACTA may damage my liver and cause serious illness or death. I must have blood tests to check my liver before I start taking PROMACTA and during treatment with PROMACTA.
    - Long-term use of PROMACTA may cause changes in my bone marrow. These changes may lead to abnormal blood cells or my body making less blood cells.
    - When I stop receiving PROMACTA, my low blood count may become worse than before I started receiving PROMACTA. This increases my risk for having a serious bleed. These effects are most likely to happen shortly after I stop PROMACTA or within 4 weeks of stopping PROMACTA.
    - I have a higher chance of getting a blood clot if my platelet count is too high during treatment with PROMACTA.
    - PROMACTA may worsen blood cancers and is not approved for use in patients with blood cancer or a precancerous condition called myelodysplastic syndrome (MDS).
- I will report any adverse events to my prescriber.
- I understand that I should not discontinue PROMACTA without talking to my healthcare provider.
- I understand that in order to receive PROMACTA, I am required to enroll in the risk management component of the PROMACTA *CARES* Program. My healthcare provider will monitor how I am doing on PROMACTA and report to PROMACTA *CARES* every 6 months about certain serious side effects, and make sure PROMACTA is right for me
- I understand that my healthcare provider will disclose personal and medical information about me to GlaxoSmithKline, its agents or contractors (together, "**GSK**"). Such information, to the extent permitted by applicable law, will be used by GSK and disclosed to third parties (e.g., Food and Drug Administration) in

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order to better understand the safety and effectiveness of PROMACTA. Further, such information (after being de-identified of my personal information) will be used by GSK to evaluate patient enrollment in, and the administration of, PROMACTA *CARES*

- I understand that, if I do not sign this Patient Enrollment Form, I will not be enrolled in the mandatory risk management component of PROMACTA *CARES* and will not receive PROMACTA.
- I understand that GSK, its agents and contractors may contact me via phone, mail, or e-mail to survey me on the effectiveness of the program requirements for PROMACTA *CARES.*

Please see the following appended materials:

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

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

- Medical Follow-up –
  - Prescribers must complete a Patient Baseline Form for each patient within 30 days of enrollment and a Medical Follow-up and Authorization Form every 6 months during treatment with PROMACTA. The Medical Follow-up and Authorization Form also requires the prescriber to authorize continued treatment with PROMACTA.
  - A PROMACTA *CARES* Call Center must remind the prescriber when it is time to complete the Medical Follow-up and Authorization Form for each patient.
  - All reported serious adverse events must be further investigated and followed by the GSK Safety department. These forms can be completed and faxed to PROMACTA *CARES* at 1-877-9-PROMACTA (or 1-877-977-6622) or completed over the telephone. Please refer to the appended Long-term Monitoring Procedure.

- Patient Discontinuation – Prescriber must notify PROMACTA *CARES* when a patient discontinues PROMACTA and complete the Discontinuation and Post-Therapy Form at the time of discontinuation and 3 months later.

Please see the following appended materials:

- PROMACTA *CARES* Long-term Monitoring Procedure
- Patient Baseline Form

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- 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

C. Implementation System

The Implementation System must include the following:

- GSK must maintain a database of all certified entities including dispensing entities (i.e., pharmacies and physician dispensing clinics), and enrolled patients to monitor and evaluate implementation of the elements provided for in II.B.2. and II.B.3.
- GSK must monitor distribution of PROMACTA to determine whether the drug is only drop-shipped to certified hospitals, pharmacies, physician dispensing clinics, and patients.
- GSK must monitor certified dispensing entities to ensure only enrolled and authorized patients are receiving PROMACTA. If a dispensing entity is found to be non-compliant with the PROMACTA *CARES* Program, GSK will prevent the dispensing entity from dispensing PROMACTA.
- Based on monitoring and evaluation of these elements to assure safe use, GSK must take reasonable steps to work to improve implementation of these elements.

D. Timetable for Submission of Assessments

A REMS Assessment must be submitted to FDA every 6 months for the first 24 months following approval, then annually thereafter.