CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-291

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-291

GlaxoSmithKline
Attention: Dennis Williams
1250 South Collegeville Road
Collegeville, PA 19426

Dear Mr. Williams,

Please refer to your new drug application (NDA) dated December 18, 2007, received December 19, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Promacta® (eltrombopag) Tablets, 25 mg and 50 mg.

We acknowledge receipt of your submissions dated December 18, 2007, January 18, February 12 and 27, March 3, 6, 14, 20 and 27, April 1, 7, 11, 14, 16, 18 and 25, May 8, 9, 13, 19, 20, 22, 23 and 30, June 4, 6, 13 and 26, July 2 and 21, August 4, 8, 11, 19, 27, 28 and 29, September 3, 5, 10, 15, 16, 22, 23, 24, 25 and 29, October 1 (2), 2, 6, 8, 14, 17 (2), 20, 21, 22 and 29, November 4 and 18, 2008.

This new drug application provides for the use of Promacta® (eltrombopag) Tablets 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.

We completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.510), effective on the date of this letter, for use as recommended in the enclosed labeling text and required patient labeling. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

ACCELERATED APPROVAL

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled trials to verify and describe clinical benefit. We remind you of your postmarketing requirements specified in your submission dated October 14, 2008. These requirements are listed below.

1. To complete trial TRA102537 entitled, "A randomized, double blind, placebo-controlled Phase 3 study, to evaluate the efficacy, safety, and tolerability of eltrombopag, a thrombopoietin

receptor agonist, administered for 6 months as oral tablets once daily in adult subjects with previously treated chronic idiopathic thrombocytopenic purpura (ITP)."

Protocol submission:	Completed
Trial start date:	Underway
Final Report Submission:	November 2009

2. To complete trial TRA108057 entitled, "An open-label repeat dosing study of eltrombopag olamine in adult subjects, with chronic idiopathic thrombocytopenic purpura (ITP)."

Protocol submission:	Completed
Trial start date:	Underway
Final Report Submission:	April 2009

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to these postmarketing requirements must be clearly designated "**Subpart H Postmarketing Requirements.**"

REQUIRED PEDIATRIC ASSESSMENTS

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

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

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute [section 505(0)(3)(A), 21 U.S.C. 355(0)(3)(A)]. This provision took effect on March 25, 2008.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(l) will not be sufficient to assess the signals of the following serious risks in patients with chronic ITP who are receiving Promacta® (eltrombopag) Tablets, specifically signals of the serious risk of bone marrow reticulin formation and bone marrow fibrosis, or to identify unexpected serious risks of adverse reactions within the fetus of pregnant woman and in the nursing infants of women who are receiving Promacta® (eltrombopag) Tablets.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) has not yet been established, and is therefore not sufficient to assess these signals of serious risks or to identify unexpected serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following studies.

3. To develop and maintain a prospective, observational pregnancy exposure registry study conducted in the United States that compares the pregnancy and fetal outcomes of women exposed to Promacta® (eltrombopag) Tablets during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, adverse effects on immune system development, platelet number and function, neoplasm formation, bone marrow reticulin formation, thrombotic events, and any serious pregnancy outcomes. These events will also be assessed among infants through at least the first year of life.

   The timetable you submitted on October 14, 2008 and November 10, 2008 states that you will conduct this study according to the following timetable:

Final Protocol Submission:	May 2009
Study Start Date:	November 2009
First Interim Report Submission:	November 2010, then annually
Final Report Submission:	November 2019

4. To conduct a milk-only lactation study in the subset of women enrolled in the pregnancy registry that choose to breastfeed their infants. This study will be designed to detect the presence and concentration of Promacta® (eltrombopag) Tablets in breast milk and any effects on milk production and composition. The study will include a symptom diary for mothers to record any adverse effects in the breastfeeding infants.

   The timetable you submitted on October 14, 2008 and November 10, 2008 states that you will conduct this study according to the following timetable:

Final protocol Submission:	May 2009
Study Start Date:	November 2009
First Interim Report Submission:	November 2010, then annually
Final Report Submission:	November 2019

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this signal of the serious risk of bone marrow reticulin formation and fibrosis.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following clinical trial:

5. To conduct trial TRA105325 entitled, "EXTEND (Eltrombopag extended dosing study): an extension study of eltrombopag olamine in adults, with idiopathic thrombocytopenic purpura (ITP), previously enrolled in an eltrombopag study." The protocol for this trial was previously submitted to FDA and the study is currently active. The protocol will be modified to include performance of bone marrow examinations prior to the initiation of Promacta® (eltrombopag) Tablets, following 12 months of Promacta® (eltrombopag) Tablets therapy as well as following the completion of 24 months of Promacta® (eltrombopag) Tablets therapy; enrollment will

continue until these data are obtained from at least 150 patients. An interim report will contain, in addition to any other items, results of bone marrow evaluations for patients who have completed bone marrow evaluations at baseline and following 12 months of Promacta® (eltrombopag) Tablets therapy.

The timetable you submitted on October 14, 2008 states that you will conduct this trial according to the following timetable:

Protocol Modification Submission:	January 2009
First Interim Report Submission:	January 2012
Final Report Submission:	January 2014

Submit the protocols to your IND 63,293, with a cross-reference letter to this NDA 22-291. Submit all final reports to your NDA. Use the following designators to prominently label all submissions, including supplements, relating to these postmarketing studies and clinical trial as appropriate:

- Required Postmarketing Protocol under 505(o)
- Required Postmarketing Final Report under 505(o)
- Required Postmarketing Correspondence under 505(o)

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Title IX, Subtitle A, Section 901 of FDAAA amends the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1 (a)). This provision took effect on March 25, 2008.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Promacta® (eltrombopag) Tablets to ensure the benefits of the drug outweigh the risks of hepatoxicity, bone marrow fibrosis, worsened thrombocytopenia and increased risk for hemorrhage after Promacta® (eltrombopag) Tablets cessation, thromboembolic complications, an increased risk of hematological malignancies, and progression of malignancy in patients with a pre-existing hematological malignancy or in myelodysplastic syndrome (MDS). Pursuant to 505-1(f)(1), we have also determined that

Promacta® (eltrombopag) Tablets can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate these risks listed in the labeling.

Your proposed REMS, appended to this letter, submitted on November 18, 2008, in response to our July 8, 2008 meeting which we informed you that a REMS is necessary to ensure that the benefits of Promacta outweigh its risks, is approved. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Information for assessment of the REMS must include:

- An assessment of use data establishing the circumstances of the use of Promacta:
    - The extent of use in the indicated population
    - The extent of use in patients by various baseline data parameters (e.g., platelet count, spleen status, number of previous therapies, duration of ITP, previous treatment with Promacta, age)
    - The extent of use for treatment of thrombocytopenia associated with chemotherapy or MDS
    - The extent of use for treatment for other reasons by diagnosis and ICD-9 code
    - The extent of use in inpatients versus outpatients
    - The extent of dispensing stratified by dispensing entity (e.g., specialty pharmacy, VA pharmacy, hospital pharmacy, physician dispensing clinic)

- An assessment of enrollment and discontinuation statistics for patients, prescribers, and pharmacies:
    - The number of patients enrolled in PROMACTA *CARES* (during the reporting period and cumulative)
    - The number of patient person-years for enrolled patients in PROMACTA *CARES*
    - The number of new patients enrolled during the reporting period
    - The number of patients who received Promacta that were not enrolled (during the reporting period and cumulative)
    - The number of patients who discontinued Promacta (during the reporting period and cumulative)
    - The number of patients who were lost-to-follow-up (during the reporting period and cumulative)
    - The number of patients who discontinue Promacta and are re-enrolled for another course of Promacta treatment (during the reporting period and cumulative)
    - The number of patients who discontinue Promacta due to a liver abnormality and are re-enrolled (during the reporting period and cumulative). This should include the number who are actually re-enrolled versus the number of patients who attempt and the prescriber declines re-enrollment.
    - The number of healthcare providers enrolled in PROMACTA *CARES* (during the reporting period and cumulative)
    - The number of new healthcare providers enrolled in PROMACTA *CARES*

- The number of healthcare providers actively prescribing Promacta during the reporting period.
- The number of healthcare providers who have ordered/prescribed Promacta who were not enrolled (during the reporting and cumulative).
- The number of pharmacies by type (e.g., specialty pharmacy, VA pharmacy, hospital pharmacy, physician dispensing clinic) enrolled in the PROMACTA *CARES* Program.
- The number of new pharmacies by type (e.g., specialty pharmacy, VA pharmacy, hospital pharmacy, physician dispensing clinic) enrolled in the PROMACTA *CARES* Program.
- The number of pharmacies by type that actively dispensed Promacta during the reporting period.
- The number of pharmacies who ordered/prescribed/dispensed Promacta that were not enrolled (during the reporting period and cumulative).

- Compliance Assessments

  - Assessment and summary of pharmacy compliance stratified by pharmacy type (e.g., specialty pharmacy, VA pharmacy, hospital pharmacy, physician dispensing clinic). This may include but not limited to Completion of the Inventory Tracking Log, prescriber enrollment, patient enrollment, documentation of each element requested on the Inventory Tracking Log.

    - The summary will include an analysis of data commonly missing or inaccurate, how GSK reconciles missing data, and an analysis of pharmacies late or not providing the Inventory Tracking Log. This summary will describe any corrective action taken.
    - The summary will include an analysis of non-compliance and describe any corrective action taken.

  - Assessment and summary of pharmacy compliance with documentation of the unique prescription verification number for each Promacta prescription, by pharmacy type.
  - Assessment of the amount of drug shipped to each site compared to the actual patient orders and summary of reconciliation. This summary will describe any corrective actions taken.
  - A summary of the pharmacy audits performed during the reporting period. This may include but not be limited to the number and specific type audited (e.g., specialty pharmacy, VA pharmacy, hospital pharmacy, physician dispensing clinic), reason for audit, description of compliance with prescriber enrollment, patient enrollment, authorization/verification, and maintenance of the Inventory Tracking Log. This summary will identify any deviations and the corrective actions taken.
  - The number and summary of pharmacies de-authorized to dispense Promacta during the reporting period and cumulative.
  - An assessment of prescriber compliance with elements of certification: completing the Patient Baseline Form, Medical and Reauthorization Form, complying with the Discontinuation Procedure, and Post-Discontinuation Follow-Up Procedures for each patient during the reporting period and cumulative.

- The number and summary of prescribers who had their ability to enroll or prescribe Promacta to new patients revoked during the reporting period and cumulative. Describe the types of non-compliance.
- The number and summary of prescribers who can no longer prescribe Promacta during the reporting period and cumulatively.

- Safety Assessments

  - 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 and analysis of the following serious adverse events reported during the reporting period including:

    - Hepatotoxicity
    - Bone marrow reticulin formation
    - Bone marrow fibrosis
    - Newly diagnosed hematological malignancy
    - Progression of previously diagnosed hematological malignancies or precancerous condition (MDS)
    - Worsening thrombocytopenia /Bleeding upon cessation of Promacta
    - Thrombotic/Thromboembolic events
    - Death

  - The total number and percentage of patients who had:

    - Hepatotoxicity
    - A bone marrow biopsy due to a change in the patient's peripheral blood smear (cumulative)
    - A diagnosis of bone marrow fibrosis (cumulative)
    - A diagnosis of a new hematological malignancy (cumulative)
    - Progression of a previously diagnosed hematological malignancy (cumulative)
    - Worsening thrombocytopenia upon cessation of Promacta (cumulative)
    - A thrombotic/thromboembolic event (cumulative).

  - Where clinical data are incomplete concerning events of interest (e.g., hepatotoxicity, bone marrow fibrosis, hematological malignancy, thrombotic/thromboembolic complications, worsened thrombocytopenia upon cessation of Promacta, and death) or data points of interest, the report will include a complete description of GSK's attempts to obtain the missing data. If necessary to establish the cause of death for a patient receiving Promacta, GSK will obtain information from the National Death Index of the National center for Heath Statistics, Centers for Disease Control.

- 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 narrative summary with analysis of reports with inpatient to outpatient (or vice versa) transition issues.
- An assessment of prescriber and patient understanding regarding the safe-use of PROMACTA (i.e., the results of surveys administered to prescribers and patients). The patient survey instrument and methodology will be developed after the product labeling and the educational materials are finalized and will be provided to the FDA for review and comment at least 2 months before it is administered to patients in the field. The survey protocol will include the sample size and confidence intervals associated with that sample size; how the sample will be determined (selection criteria); the expected number of patients to be surveyed; how the participants will be recruited; how and when the surveys will be administered; and an explanation of controls used to minimize bias.
- A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
- Based on the information reported, an assessment and conclusion of whether the REMS is meeting its goals, and whether modification to the REMS are needed.

Prominently identify the amendment containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

- **NDA 22-291 REMS ASSESSEMENT**
- **NEW SUPPLEMENT FOR NDA 22-291 REMS ASSESSMENT PROPOSED REMS MODIFICATION**

Please note that:

- This Medication Guide must be reprinted immediately following the last section of labeling or, alternatively, accompany the prescription drug labeling [21 CFR 201.57(c)(18)] or [21 CFR 201.80(f)(2)];
- You are responsible for ensuring that this Medication Guide is available for distribution to every patient who is dispensed a prescription for this product [21 CFR 208.24];
- The final printed Medication Guide distributed to patients must conform to all conditions described in 21 CFR 208.20, including minimum of 10 point text; and
- You are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided [21 CFR 208.24(d)].

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert, Medication Guide) and/or submitted labeling (package insert submitted October 29, 2008 and Medication Guide submitted on October 17, 2008). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 22-291."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed container labels that are identical to the enclosed immediate container labels and/or submitted immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-291**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROMOTIONAL MATERIALS

As part of the approval under Subpart H, we acknowledge that you have submitted to the Agency your promotional materials (both promotional labeling and advertisements) that are to be used within the first 120 days after approval. In addition, as required by 21 CFR 314.550, submit all promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of all promotional materials directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Please submit one market package of the drug product when it is available. Please submit final promotional materials with FDA Form 2253 to the above address at the time of initial dissemination of the labeling or at the time of initial publication of the advertisement.

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

We acknowledge your November 4, 2008 commitment to expedited reporting of bone marrow fibrosis and new malignancies/progression of malignancies with Promacta® (eltrombopag) Tablets.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Hyon-Zu Lee, Pharm.D., Regulatory Project Manager, at 301-796-2050.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

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

/s/

Richard Pazdur
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