CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-291

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	November 19, 2009
From	Richard Pazdur, MD
Subject	Office Director Memo
NDA/BLA #	22-291
Applicant Name	GlaxoSmithKline
Date of Submission	December 19, 2007
PDUFA Goal Date	September 19, 2008
Proprietary Name / Established (USAN) Name	Promacta™ Eltrombopag tablets
Dosage Forms / Strength	25 and 50 mg tablets
Proposed Indication(s)	"Promacta is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy."
Action/Recommended Action for NME:	Approval under accelerated approval regulations (21 CFR 314.510) "Subpart H"

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Review	Andrew Dmytrijuk, MD & Kathy Robie Suh, MD PhD (TL); Division Director Review—Dwaine Rieves, MD
Statistical Review	Qing Xu, PhD & Jyoti Zalkikar, PhD (TL)
Pharmacology Toxicology Review	Yash Chopra, PhD & Adebayo Laniyonu, PhD (TL)
CMC Review/OBP Review	Sue-Ching Lin, PhD & Ying Wang, PhD
Microbiology Review	not applicable (oral tablet)
Clinical Pharmacology Review	Joseph Grillo, PharmD & Young Moon Choi, PhD (TL)
DDMAC	Carrie Newcomer, PharmD (med guide review) Sean Bradley (other labeling)
DSI	John Lee, MD & Tejashri Purohit-Sheth, MD
CDTL Review	none (submission predated need for CDTL)
OSE/DMETS	Walter Fava, RPh & Linda Kim-Jung, PharmD

OSE/DDRE	Suzanne Berkman, PharmD, Mary Dempsey, Claudia Karwoski, PharmD
Pediatric and Maternal Health	Richardae Araogo, PharmD, Karen Feibus, MD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader
TL = Team Leader

Eltrombopag is an orally-administered thrombopoietin receptor agonist that stimulates bone marrow megakaryocytes to produce platelets. The approval was based upon controlled clinical study data obtained over a six week treatment period and multiple months of treatment in a single arm extension study. Continuing and recently completed studies will assess the long term safety and clinical benefit of eltrombopag

The safety and efficacy of eltrombopag were evaluated in two double-blind, placebo-controlled clinical studies of 231 adult patients with chronic ITP who had completed at least one prior ITP therapy and who had baseline platelet counts < 30,000/mcL, including patients who may have undergone splenectomy. In one study patients were randomized to either placebo or one of three doses of eltrombopag, 30, 50 or 75 mg. In the other study, patients were randomized to either placebo or eltrombopag 50 mg. Eltrombopag and placebo tablets were administered daily for six weeks. Elthrombopag was discontinued if platelet counts exceeded 200,000/mcL. Patients were observed for six weeks following discontinuation of the study drugs.

The primary endpoint in both studies was "response rate," defined as an increase from the baseline platelet count to a count $\geq$ 50,000/mcL. Eltrombopag 50 mg administration resulted in response rates of 59 and 70% in each study, compared to placebo response rates of 16 and 11% ($p < 0.01$ for the treatment difference in each study). Eltrombopag response rates were similar irrespective of whether a previous splenectomy had been performed. Overall, seven patients (three in the placebo and four in the eltrombopag groups) underwent hemostatic challenges, such as surgical procedures. Additional ITP medications were required in all placebo patients and none of the eltrombopag patients.

Eltrombopag was administered to 109 patients in an open label, extension study; 74 received the drug for at least three months, 53 for at least six months and three for at least one year. At baseline, the median platelet count was 18,000/mcL. Median platelet counts were 74,000, 67,000 and 95,000/mcL, at three, six and nine month follow-up time points, respectively.

Overall, 313 patients with chronic ITP were exposed to eltrombopag. The clinical studies identified risks for hepatotoxicty, worsened thrombocytopenia (compared to baseline) and hemorrhage following eltrombopag discontinuation, and a risk for cataracts. Potential risks for TPO receptor agonists include bone marrow reticulin formation and

marrow fibrosis during long term therapy and a risk for thromboses due to excessive platelet increases.

The risk for hepatotoxicity is cited as a boxed warning. In the controlled clinical studies, one patient experienced grade 4 (NCI Common Terminology Criteria for Adverse Events) elevations in serum liver test values during eltrombopag therapy, worsening of underlying cardiopulmonary disease, and death. No placebo group patients experienced grade 4 liver test abnormalities. Overall, serum liver test abnormalities (predominantly grade 2 or less in severity) were reported in 10 and 8% of the eltrombopag and placebo groups, respectively.

The controlled clinical studies also noted a risk for worsened thrombocytopenia and hemorrhage following eltrombopag discontinuation. Transient platelet count decreases to levels below baseline were observed following study drug discontinuation in 10% of the eltrombopag and 6% of the placebo groups. Serious hemorrhagic events requiring the use of supportive ITP medications occurred in 3 severely thrombocytopenic patients within one month following eltrombopag discontinuation; none were reported within the placebo groups.

In the controlled clinical studies, cataracts developed or worsened in 5% of the patients who received eltrombopag 50 mg daily and 3% of the placebo-group patients. Cataracts were also observed in non-clinical rodent toxicology studies..

The most common adverse reactions that occurred more frequently in the eltrombopag groups compared to the placebo groups consisted of nausea, vomiting, mennorrhagia, myalgia, paresthesia and cataracts. These reactions occurred in 3 to 6% of the eltrombopag patients and were generally mild to moderate severity.

The recommended starting dose of eltrombopag is 50 mg once daily for most patients. For patients of East Asian ancestry or patients with moderate or severe hepatic insufficiency, the starting dose is 25 mg once daily. The eltrombopag dose is adjusted to achieve platelet counts $\geq$ 50,000/mcL as necessary to reduce the risk for bleeding. Eltrombopag should not be used in an attempt to normalize platelet counts.

Only prescribers enrolled in the PROMACTA *CARES* Program may prescribe eltrombopag. The risk managment program is described below.

Major Features of the REMS:

a. A medication guide—to be dispensed concomitant with the drug.

b. FDA-approved communication plan to include specific text for healthcare provider materials and institutional materials. The education process (as well as prescriber certification/patient registry) is referred to as the "*Promacta Cares* " program.

c. Elements to assure safe use: drug distribution is limited to prescribers and patients who enroll in the *Promacta Cares* program.

-all prescribers must be "certified" by the company; certification involves signing a specific document (prescriber enrollment form) that attests to familiarity with the labeling and agreement to comply with the expectations of the program/patient registry.

-To comply with the registry/program, prescribers must:

-sign and submit the "healthcare provider enrollment form"
-at enrollment of a patient, complete a "patient enrollment form" and "patient baseline data form."
-obtain signature of each patient to confirm participation in the program/disclosure of information to the program
-complete a form every six months to verify that continued treatment is appropriate and to actively solicit (yes/no, check list) major safety outcomes using a
-complete a "patient discontinuation" form if eltrombopag is discontinued; a post-discontinuation form must also be completed — months later — months after drug discontinuation).

b(4)

The REMS does not prohibit prescription of eltrombopag for non-ITP uses; however, all clinical use of the drug is tracked through the program. Similarly, the REMS

The REMS assessments are to be performed frequently for the first two years following product launch and regularly thereafter.

Consideration of Accelerated Approval:

The review team worked with the company to develop an indication for eltrombopag to be used as a chronic ITP therapy among relatively refractory patients. This indication is based upon the two phase 3 clinical studies of six weeks duration plus the supportive information from the single arm extension study. To reiterate, the recommendation for Subpart H approval is based upon:

a) use of the "short term" platelet count response as a surrogate marker for longer platelet count responses (platelet counts are recognized as acceptable measures of clinical benefit for patients with chronic ITP)

b) chronic ITP is a serious medical condition

c) eltrombopag approval would provide a meaningful therapeutic benefit to patients over existing treatments because of its minimal risk for immunogenicity (based upon the small molecule characteristics). The labeling for romiplotim, the only currently marketed TPO receptor agonist, includes information regarding the risks for immunogenicity. These

risks are not applicable to eltrombopag. As noted above, eltrombopag response rates were similar irrespective of whether a previous splenectomy had been performed. In contrast, trials with romiplotim had fewer responses in the population of patients who underwent prior spelenectomy compared to non-splenctomized patients.

Post-marketing Requirements (PMR):

The PMR are outlined below and specifically include submission of the report for the RAISE study (a study that provides longer term exposure data in a controlled setting and that should be sufficient to address the accelerated approval expectation for a confirmatory study) and the modification of the on-going extension study to obtain baseline and follow-up bone marrow results.

1. To submit the complete study report for Study 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)" (the "RAISE" study).

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

3. To conduct Study 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 study protocol will be modified to include performance of bone marrow examinations prior to the initiation of eltrombopag, following 12 months of eltrombopag therapy as well as following the completion of 24 months of eltrombopag therapy; study 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 eltrombopag therapy.

4. 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 eltrombopag 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. Annual interim reports will

be submitted until [redacted] b(4)

5. 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 eltrombopag 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. Annual interim reports will be submitted until [redacted] b(4)

Regulatory Recommendation: Accelerated Approval

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/s/

Richard Pazdur
11/20/2008 09:37:17 AM
MEDICAL OFFICER