CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207027Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	See electronic date stamp
From	Janice Brown M.S.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	207027
Applicant	GlaxoSmithKline LLC
Date of Submission	February 24, 2015
PDUFA Goal Date	August 24, 2015
Proprietary Name / Established (USAN) names	eltrombopag
Dosage forms / Strength	for oral suspension, 25 mg
Proposed Indication(s)	PROMACTA is a thrombopoietin receptor agonist indicated for the treatment of: 1. thrombocytopenia in adult and pediatric patients 1 year and older with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. 2. thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. 3. patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.
Recommended:	Regular Approval, pending an acceptable facility inspection and agreement on the proposed labeling and PMCs

Include the following statement in the action letter:

A shelf life of 24 months is granted for PROMACTA (eltrombopag) for oral suspension, when stored at 25°C (77°F); excursions permitted 15°C to 30°C (59 to 86°F)

1. Introduction

Eltrombopag (Promacta) is an orally available small molecule thrombopoietin receptor (TPOR) agonist currently indicated for the treatment of thrombocytopenia in adult and pediatric patients 6 years and older with chronic immune (idiopathic) thrombocytopenia (ITP) who has had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

This New Drug Application (NDA) is being submitted in response to a Pediatric Written Request under the Best Pharmaceuticals for Children Act. This NDA seeks a new indication in children and provides CMC data supporting a new dosage form, Promacta (eltrombopag) for oral suspension. This NDA is seeking to expand the indication of eltrombopag to include children ages 1 and older, based on data from ages 1-5 years old children that received eltrombopag for oral suspension in the PETIT and the PETIT2 studies. In the PETIT studies, subjects in the older age cohorts (ages 6 to 17 years) received tablets; subjects in the youngest age cohort (ages 1 to 5 years) received the oral suspension. Clinical data to support the indication in children aged 6 years and older using the approved tablet strengths (12.5 mg, 25 mg, 50 mg, and 75 mg) was reviewed in NDA 022291/S-015 (sequence no. 170). Supplement 015 was approved in June 2015. Module 5 of this NDA submission is identical to module 5 in NDA 022291/S-015. A new NDA was submitted since eltrombopag for oral suspension is a new dosage form of Promacta.

Eltrombopag for oral suspension 25 mg, is an elongated stickpack containing reddish-brown to yellow powder, which when reconstituted with water, forms a reddish-brown suspension. Multiple strengths can be made by adding 1, 2, or 3 stickpacks to achieve the required dose range of 25 mg/day to a maximum dose of 75 mg/day. The eltrombopag for oral suspension is prepared with water only since there is a significant lowering of the bioavailability of eltrombopag when taken with food or other medications containing polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, and zinc. The suspension is prepared by adding twenty milliliters of water to the supplied mixing bottle and the contents of the prescribed number of packets (depending on the recommended dose) is added, followed by shaking the bottle for at least 20 seconds to mix the water with the powder. Patient dosing is achieved by withdrawal and administration of the suspension using a provided 20 mL syringe.

The Office of Orphan Products Development granted Orphan Drug Designation in May 2008 for eltrombopag for the treatment of ITP (ODA # 07-2519). The Applicant requested priority review per MaPP 6020.3, which states "supplemental applications that propose labeling changes pursuant to a final pediatric study report will automatically receive a priority review designation." The Division granted priority review for this NDA submission.

2. Background

A complete background was summarized in Virginia Kwitkowski' s CDTL review for NDA 22291, S-015 (dated June 5, 2015) and will not be repeated in this review.

3. CMC

In the NDA, the applicant refers to the drug product name as Promacta (eltrombopag) (b) (4) for oral suspension (PfOS). The name has been changed to Promacta (eltrombopag) for oral suspension consistent with the USP Nomenclature Guidelines. PfOS refers to Promacta for oral suspension in this CDTL review.

DRUG SUBSTANCE REVIEW - CMC information for eltrombopag olamine referenced NDA 022291. With the exception of S.4.4 Batch Analyses, reference is made to NDA 022291 for CMC information for eltrombopag olamine. No drug substance changes were made for the new PfOS formulation.

Drug substance characteristics - The drug substance is eltrombopag olamine, a small molecule thrombopoietin (TPO) receptor agonist for oral administration. The drug substance is (b) (4) The aqueous solubility of eltrombopag olamine is greatly affected by pH. It is practically insoluble in aqueous buffer across a pH range of 1 to 7.4. (b) (4) of eltrombopag olamine has been observed to date. (b) (4) Eltrombopag olamine does not contain any chiral centers and therefore has no optical activity. In solution, the compound is stable at neutral or acidic pH, but becomes chemically unstable at higher pH. The particle size is a critical quality attribute (CQA) of the drug substance to ensure acceptable drug product performance.

Manufacture of the drug substance - Eltrombopag olamine (b) (4)

(b) (4)

Retest Period, Storage Conditions - A drug substance has a retest period of (b) (4)

DRUG PRODUCT REVIEW - PfOS, 25 mg, is an elongated stickpack containing reddish-brown to yellow powder, when reconstituted with water, forms a reddish-brown suspension. Each stickpack delivers (b) (4) eltrombopag olamine equivalent to 25 mg of eltrombopag free

acid and the inactive ingredients mannitol, sucralose, and xanthan gum. PfOS is reconstituted with water into a suspension prior to administration.

The inactive ingredients in PfOS are mannitol, sucralose, and xanthan gum. If three stickpacks were required as a single 75 mg dose, the maximum amount of excipients is either within the IID (xanthan gum) or was found acceptable by the nonclinical reviewer (mannitol and sucralose). The specifications of the inactive ingredients for mannitol, sucralose, and xanthan gum comply with the USP/NF and Ph. Eur. The drug product contains mannitol at (b) (4)% w/w of the formulation. Mannitol was selected for use (b) (4) in this formulation to ensure the appropriate characteristics of the powder are obtained. PfOS is a dry powder mixture containing (b) (4)

(b) (4)

Manufacture of the drug product - PfOS is manufactured by (b) (4)

(b) (4)

(b) (4) Filled eltrombopag PfOS stickpacks, 25 mg, are packaged in a carton, and is further assembled in a larger carton with the auxiliary components (40 cc reconstitution bottle, closure with syringe-port capability, and 20 mL oral dosing syringe).

Drug Product Specification - The finished product specification includes tests for description, identity (HPLC), eltrombopag content (HPLC), uniformity of dosage units (HPLC), impurities (HPLC), dissolution (PhEur/USP/JP), and microbial enumeration (PhEur/USP/JP). Batch analysis data provided comply with the specifications and indicate consistent and reproducible manufacture.

Stability of the drug product - A shelf life of 24 months is granted for PROMACTA (eltrombopag) for oral suspension, when stored at 25°C (77°F); excursions permitted 15°C to 30°C (59 to 86°F).

Following reconstitution, administer the product immediately, within 30 minutes of reconstitution when held at 25°C (77°F); excursions permitted 15°C to 30°C (59 to 86°F) [See USP Controlled Room Temperature].

No CMC issues which preclude approval were found and the drug substance and drug product reviewer (Danuta Gromek-Woods, Ph.D.) recommended approval of the NDA. The process reviewer (Xuhong Li, Ph.D.) concluded, that the commercial manufacturing process and control strategy were appropriately developed and adequately described.

CDRH REVIEW - Each kit contains 30 packets of PfOS, 25 mg and co-packaged in a kit with a 40-cc reconstitution vessel, an oral dosing syringe, and a threaded closure with syringe-port capability. The oral dosing syringe and threaded bottle closure with syringe port capability are registered by the component manufacture with the FDA's Medical Device database under product code (b) (4) These components are categorized as class I cGMP exempt medical devices.

Testing - Testing included biocompatibility and performance testing. A summary of the analysis is bulleted below.
• Component compatibility and resistance to separation
• Dose accuracy of the syringe
• Freedom from leakage
• Force required to attach and detach system components
• Functionality after aging and shipping
• Biocompatibility of the components
• Review of Instructions of Use.

The CDRH reviewer (Janice Polacek, DARRTS entry on 29-Jul-2015) found the applicant's evaluation of the reconstitution vessel, adapta-cap and oral syringe, acceptable for use and recommended approval of the NDA submission.

FACILITY REVIEW –The following facility recommendations are pending as of August 4, 2015.

- SMITHKLINE BEECHAM LIMITED (CORK) – Drug substance manufacturer
- GLAXO OPERATIONS UK LIMITED – Drug product manufacturer
- GLAXO OPERATIONS UK LTD - Control testing laboratory

The facility reviewer (Zhong Li, Ph.D.) stated that the OPF recommendation is pending. As a result of the pending facility recommendation, no final action was made for this NDA. The facility review is also pending.

BIOPHARMACEUTICS REVIEW - The Applicant provided adequate information/data on dissolution method development to justify the selection of the 50 mM potassium phosphate pH 6.8 buffer with 0.2% polysorbate 80 at 50 rpm. Although the reconstitution of the sample in 0.1 N HCl prior to introduction into the dissolution vessels is not clinically relevant, the

procedure is acceptable because [redacted] (b) (4) which in turn minimizes the variability in the dissolution profiles.

No issues which preclude approval were found and the biopharmaceutics review (Banu Zolnik, Ph.D.) recommended approval of the NDA.

MICROBIOLOGY REVIEW – The drug product microbial release testing complies with USP <61> for total aerobic microbial count and total yeast and mold count. The acceptance criteria agree with the recommendations in USP <1111> for non-aqueous preparations for oral use. The selective test for *E. coli* was not included in the specification due to shown antimicrobial activity present in the product which inhibits the growth of this microorganism.

The applicant has sufficiently demonstrated the integrity of the container-closure system, used in the commercial production of the drug product, per the Agency's recommendation as a microbial barrier.

The Division of Microbiology Assessment has reviewed NDA 207027 for Eltrombopag for oral suspension, 25 mg, and found the microbiology information acceptable and recommended approval of the NDA submission (see microbiology review by Jonathan G. Swoboda, Ph.D.).

OFFICE OF TESTING AND RESEARCH (OTR) REVIEW – The OTR reviewer, Arzu Selen, Ph.D., had the following recommendations in her review dated July 14, 2015 (final signature July 14, 2015 in Panorama) for this NDA.

1. The appropriate dosing time window and the dosing recommendations for the eltrombopag PfOS should be provided for infants 2 years old and younger considering that dosing recommendations would be significantly different than that for adults as most of their diet is high in calcium and the recommended time window for adults would not apply to pediatrics who have different dietary needs and are fed frequently.

2. Without the appropriate labeling language, availability of both the powder for oral suspension and PROMACTA tablet in the market and allowing them to switch between the dosage forms may lead to problems. Administering the 12.5 mg tablet will be easier than trying to get 12.5 mg from the 25 mg powder stickpack. However, this may require crushing of the tablet and mixing it into soft-food or liquids. It is possible that while some soft foods and liquids may reduce the intended dose due to chelation, other factors not assessed yet, such as binding to other food components, may also contribute to additional reduction in eltrombopag exposure.

   For the labeling, the Applicant should carry out compatibility studies (as listed under potential assessments) for the PROMACTA tablets in soft foods and liquids, even to indicate that certain soft foods such as dairy products should not be used as vehicles, and compare the recovery from the tablets with the recovery from the PfOS prepared as instructed in the labeling. While this information may be perceived as negative information for the labeling, the quantitative assessment of the extent of reduction in eltrombopag exposure due to chelation and other possible factors when mixed into soft

foods and liquids is informative and should be provided as the rationale for the recommendation. In addition, if there are cases where eltrombopag dosage forms can be mixed with acceptable vehicles (soft foods and liquids) prior to its administration, availability of this information in the drug product labeling can optimize its use by the caregiver and the patient.

CDTL comments and labeling revisions to address OTR recommendations:
Regarding OTR recommendation #1: Promacta for oral suspension is indicated for children 1 year of age and older. The review team felt it was unnecessary to specifically address a dosing time window for 1-2 year olds. Dosing recommendations are included in section 2.4 in the Full Prescribing Information. The Medication Guide also includes the statements, "Take PROMACTA on an empty stomach, either 1 hour before or 2 hours after eating food. Take PROMACTA at least 2 hours before or 4 hours after eating dairy products and calcium-fortified juices." Including dosing time recommendation in the label may not be appropriate for all situations for 1 -2 year olds. The proposed label allows administration flexibility either at bedtime or during the day.

Regarding OTR recommendation #2: PfOS and the tablet formulations are not bioequivalent. Since Promacta is a prescription product, the physician only prescribes the oral suspension or tablet. Switching between the oral suspension and tablet, requires more frequent monitoring to assess platelet counts so it is unlikely that switching between dosage forms would occur more than once. To address the concern of crushing the tablet or taking the oral suspension and mixing it into soft-food or liquids the following statement was added to section 2.4-Administration in the full prescribing information:

"Do not crush tablets and mix with food or liquids. Prepare the oral suspension with water only."

The Instructions for Use includes the following statement:

"PROMACTA powder must be mixed with water only."

Since there is a significant food effect in foods containing polyvalent cations, the current labeling states that Promacta should be taken on an empty stomach (1 hour before or 2 hours after a meal). The review team agreed that young children require more frequent feedings than adults. Non-compliance with fasting recommendations may lead to reduced drug exposure and ineffective therapy. Since this product will be taken by young children, mixing in soft foods may allow better compliance. As a result, a post marketing commitment is requested to conduct in-use stability studies using a crushed tablet and the powder for oral suspension in foods or drinks that do not contain polyvalent cations (e.g. applesauce, juice, etc.). Refer to item 13 in this review under Recommendation for other Postmarketing Study Commitments.

There is a theoretical risk that parents of children using Promacta at 12.5 mg daily will prepare a 25 mg stickpack, administer 12.5 mg, and instead of discarding the remaining 12.5 mg suspension, save it for the next day's dose. The clinical and clinical pharmacology reviewers recommended the development of a12.5 mg strength in the event a dose reduction or

incremental dose adjustments of 12.5 mg are required. Refer to item 13 in this review under Recommendation for other Postmarketing Study Commitments.

4. Nonclinical Pharmacology/Toxicology

No pharmacology/toxicology studies were submitted in the NDA. The Pharmacology/Toxicology Review (Ramadevi Gudi, Ph.D., final signature August 8, 2015) stated, "The approvability of the PfOS developed for pediatric patients 1 to 5 years of age will be deferred to product quality and clinical teams."

5. Clinical Pharmacology/Biopharmaceutics

Clinical pharmacology data included the results from a population pharmacokinetic (PK) and population pharmacokinetic/pharmacodynamic (PK/PD) analysis in pediatric chronic ITP subjects. Results were also presented for a relative bioavailability and food effect study (TRA111718).

The following narrative is from the executive summary of the Clinical Pharmacology review of this submission.

The primary Clinical Pharmacology review was conducted by Jee Eun Lee, Ph.D. concluded that "The Office of Clinical Pharmacology have reviewed the information submitted in the NDA and recommended approval of Promacta (eltrombopag) for the treatment of (b) (4) pediatric patients 1 to 5 years of age with chronic immune (idiopathic) thrombocytopenia (ITP) to increase platelet counts and reduce or prevent bleeding. We recommend a starting dose of 25 mg once daily."

Initial Dosing regimen
The recommended initial dose for pediatric patients 1 to 5 years with chronic immune (idiopathic) thrombocytopenia (ITP) is 25 mg QD. The doses will be then titrated to target platelet counts for individual patients.

Labeling
The Clinical Pharmacology team contributed to revising the Applicant's proposed labeling.

The Clinical Pharmacology reviewer recommended a Phase 4 commitment to develop a 12.5 mg strength of the PfOS formulation in order to enable the required dose adjustments to achieve target platelet counts. Currently available dispensing unit for oral suspension is 25 mg only which is not desirable for adequate dose titration in pediatric patients.

Clinical Pharmacology Findings - The studied and the applicant's proposed initial doses of eltrombopag in pediatric patients 1 to 5 years are summarized in the table below.

Population	Studied dose	Applicant's proposed dose
Non-East Asian ancestry	0.7, 1.2 and 1.5 mg/kg daily	25 mg daily

East Asian (EA) ancestry	0.5 and 0.8 mg/kg daily	(b) (4)

Dr. Lee did not agree with the applicant's proposal (b) (4) Since the majority of patients in clinical trials required doses of greater than 50 mg to achieve target platelet count, a starting daily dose of 25 mg (QD) for all pediatric patients ages 1-5 years is recommended. Dr. Lee's recommendation is intended to simplify the dosing regimen and minimize the number of dose titration required to achieve target platelet counts. Furthermore, the reviewers have concerns regarding the large fluctuation of eltrombopag concentration (b) (4)

Biopharmaceutics - PfOS and the tablet formulations are not bioequivalent. Since PfOS is not bioequivalent to the tablet formulations, the applicant proposes that platelet counts be monitored weekly for 2 weeks when a patient switches between formulations. The applicant proposes that eltrombopag be administered at least 2 hours before and at least 4 hours after polyvalent metal cation-containing products (such as antacids, mineral supplements, and dairy) based on findings from a food effect study with PfOS (TRA111718).

Study TRA111718 also included the assessment of the relative bioavailability of PfOS compared to tablet formulation in healthy adult subjects, and found that AUC of eltrombopag was increased by 22% and Cmax by 31% compared to the tablet formulation. The population PK analysis estimated about 71% of relative bioavailability of PfOS in pediatric patients 1 to 5 years of age, however, the review team conclude that the results obtained from Study TRA111718 would be more reliable since the effect of PfOS on eltrombopag PK was confounded by the effect of age as only pediatric patients 1 to 5 years of age received the PfOS in the PETIT and PETIT2 trials.

Pharmacokinetics/Pharmacodynamics - Pharmacokinetics and pharmacodynamics of eltrombopag in pediatric patients were characterized in two studies (PETIT and PETIT2) where older age group of pediatric patients (≥6 years) were also enrolled along with the target age groups. The population PK and PKPD analyses in pediatric ITP patients 1 to 17 years of age enrolled in studies PETIT and PETIT2 are summarized as followings:

- Plasma eltrombopag PK following repeat oral administration to pediatric subjects with ITP were adequately described by a 2-compartment model with first order absorption and elimination.
- Plasma eltrombopag clearance (CL/F) and volume of distribution (Q, V2/F, V3/F) parameters increased with increasing body weight. Mean plasma eltrombopag CL/F was 30% lower in East/Southeast Asian subjects compared to other races. These CL/F differences translate to mean AUC (0-tau) increases of 43% in Ease Asian subjects.
- Platelet count response following eltrombopag dosing was described by the 7-compartment life-span model (3 PK and 4 PD compartments), where the increase in platelet precursor production rate was linearly related to eltrombopag concentration.
- The majority of subjects (96%) were identified as responding to eltrombopag treatment.

- Platelet maturation rate constant increased with increasing age, which influenced the time to steady-state platelet count. The time to ≥80% of steady-state platelet count was 4 weeks.
- No significant covariates were identified on pharmacodynamics. No effect of formulation on pharmacodynamics of eltrombopag was detected.

PKPD Simulation for Justification of Initial Dosing Regimens - The applicant proposes to label a different dosing regimens from the dosing regimens evaluated in the clinical trials. The studied dosing regimens were based on body weight (1.2 mg/kg QD for non-East Asian and 0.8 mg/kg QD for East Asian in PETIT2) while the applicant's proposed dosing regimens are fixed doses (25 mg QD for non-East Asian (b) (4) for East Asian). The justification for the proposed dosing regimen was based on simulations with the PKPD model to predict platelet counts following various initial dosing regimens. This approach appears reasonable with adequate PKPD modeling evaluation. Considering the fact that the proposed dosing regimen is only for the initial dose and individual dose is to be titrated based on platelet counts, the proposal of initial dose based on simulation is readily agreeable. Among those evaluated initial doses, 25 mg QD for patients with non-East Asian ancestry (b) (4) for patients with East Asian ancestry were proposed by the applicant. For consistency in terms of dose reduction for patients with East Asian ancestry due to the lower clearance compared to patients with non-East Asian ancestry, half of the dose for non-East Asian may be adequate for the patients with East Asian ancestry. However, reviewers do not agree with the sponsor's proposed dose (b) (4) for patients with East Asian ancestry. The predicted median platelet counts following 25 mg QD for 10 weeks without dose adjustment could be close to 40 Gi/L for patients with either East Asian ancestry or non-East Asian ancestry (Figure 1). As shown in Figure 1, the (b) (4) could lead to lower platelet counts (b) (4) in East Asian without dose titration. Nonetheless, dose is likely to increase to target platelet counts to ≥50 Gi/L (b) (4) still does not appear to be desirable. The large fluctuation (b) (4) is also of concern regarding steady input of the drug for desirable drug effect. Some patients may have greater than (b) (4) times higher Cmax compared to Cmin with (b) (4).

The CDTL and clinical team agreed with the dosing recommendations.

6. Clinical Microbiology

No Clinical Microbiology review was required for this NDA.

7. Clinical/Statistical- Efficacy

Data supporting this indication comes from the results of the PETIT (**PE**diatric patients with **T**hrombocytopenia from **ITP**) studies. The Phase III PETIT 2 (TRA115450) and Phase II PETIT (TRA108062) studies are randomized, placebo-controlled, multi-center studies designed to evaluate the efficacy and safety of eltrombopag in pediatric patients with chronic ITP who have had an insufficient response to prior therapy.

The primary clinical reviewer for this application is Lori Ehrlich, M.D., Ph.D. Dr. Ehrlich recommends regular approval for eltrombopag for the treatment of thrombocytopenia in adult and pediatric patients' ≥1 years old with chronic idiopathic thrombocytopenia (ITP) who has had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. The dose proposed is as follows:

- The starting dose for adult and pediatric patients ≥6 years old is 50 mg orally once daily. If the platelet count is less than 50 Gi/L following two weeks of treatment, the dose is increased to 75 mg once daily. If the platelet count is 200-400 Gi/L, the dose is decreased by 25 mg. If the platelet count is > 400 Gi/L, the dose is held until platelet count is <150 Gi/L and reinstated at a daily dose reduced by 25 mg.
- The starting dose for pediatric patients ≥1 years old to 5 years old is 25 mg orally once daily. The dose of eltrombopag in this patient population may be increased to 50 mg orally once daily if the platelet count is less than 50 Gi/L after 2 weeks, then the dose is adjusted as above.
- For patients of East Asian ancestry in all age groups, the starting dose is 25 mg orally once daily. The dose of eltrombopag in this patient population may be increased to 50 mg orally once daily if the platelet count is less than 50 Gi/L after 2 weeks, then the dose adjusted as above.
- If the patient is at a dose of 25 mg orally once daily using the tablets or powder for oral suspension, and the platelet count is 200-400 Gi/L, the dose is decreased to 12.5 mg daily.

Dr. Ehrlich's rationale for these recommendations can be found in section 1.1 of her clinical review.

Postmarket Commitments - Dr. Ehrlich has recommended the following PMCs:

1. Develop a 12.5 mg strength stickpack for the powder for oral suspension to provide for an additional dosing for patients needing less than the current lowest dose option of 25 mg. The 12.5 mg strength is needed in the event a dose reduction or incremental dose adjustments of 12.5 mg are required. There is a concern that caregivers would use a portion of the reconstituted 25 mg stickpack and store the remaining product for later administration the following day to avoid wasting the prepared suspension. A genotoxic impurity (b) (4) forms above the level of threshold of toxicological concern (TTC) (b) (4) following reconstitution of the powder in the stickpack. To avoid the potential for storing the reconstituted drug product and ingestion of a product with genotoxic impurities, a lower strength is needed. The development of the 12.5 mg strength would avoid the need to waste half of the prepared product.

2. Conduct in-use stability studies using a crushed tablet and the powder for oral suspension in foods or drinks that do not contain polyvalent cations (e.g. applesauce, juice, etc.) to explore possible food effects on absorption. Since there is a significant food effect in foods containing polyvalent cations, the current labeling states that Promacta should be taken on an empty stomach (1 hour before or 2 hours after a meal). Young children require

more frequent feedings than adults. Non-compliance with fasting recommendations could lead to reduced drug exposure and ineffective therapy. Since this product will be taken by young children, mixing in soft foods may allow better compliance.

Efficacy Summary - Both pediatric clinical trials met their primary efficacy endpoint, and eltrombopag was shown to be efficacious in raising the platelet counts of pediatric patients ages 1 to 17 with chronic ITP. Evaluation of the secondary endpoints in both studies also favored eltrombopag over placebo. Pooled data from both trials from similar endpoints supported the individual study results. In both studies, the cohort 1 (12 to 17 years) had the highest proportion of responders with fewer responders in cohort 2 (6 to 11 years), and even fewer in the youngest cohort 3 (1 to 5 years); however, the drug was active in all age groups. [Source, *Primary Clinical Review, Section 6]*

A detailed discussion of the PETIT and PETIT 2 studies can be found in the CDTL review by Virginia E. Kwitkowski, MS, ACNP-BC, Clinical TL for NDA 22291, S015 and the primary clinical review for this NDA by Lori Ehrlich, M.D., Ph.D.

The primary statistical review was conducted by Chia-Wen Ko, Ph.D. The concurring reviewers were her Team Leader is Lei Nie, Ph.D. and Rajeshwari Sridhara, Ph.D. (Division Director). Dr. Ko's review (finalized on July 14, 2015) states that "Because data on all age cohorts have been reviewed in the NDA22291/S-015 application for an evaluation of treatment efficacy in the overall studied pediatric population, a separate statistical review for this new application is not necessary. Interested readers may refer to the NDA022291/S-015 statistical review, for details on the PETIT and PETIT2 study design and efficacy results. As assessed in the NDA22291/S-015 review, results from the PETIT and PETIT2 studies demonstrated treatment efficacy of eltrombopag in the studied pediatric population, including the 1-5 years age cohort. The proposed indication expansion therefore should be granted. The product label is to be revised to include results from the youngest age cohort in the two studies."

CDTL Comment: The clinical team leader and I concur with Dr. Ehrlich and Dr. Ko's conclusions. There are no outstanding issues that would preclude approval of this NDA submission.

8. Safety

The safety profile in pediatric patients is similar to that seen in adult patients. No new safety signals were identified in the pediatric pivotal trials. There was no difference in the frequency of all grade Adverse Reactions (ARs) between treatment arms in all age cohorts. The common ARs that occurred more frequently in patients treated with eltrombopag were upper respiratory tract infection, nasopharyngitis, cough, diarrhea, rhinitis, abdominal pain, oropharyngeal pain, toothache, rash, AST increased, and rhinorrhea. These ARs tended to be low grade, and Serious Adverse Reactions (SARs) were uncommon. There were no deaths in either pediatric trial, and evaluation of ARs of special interest did not reveal any safety signal in pediatric patients treated with eltrombopag. [*Source, Primary Clinical Review; Section 7*]

CDTL Conclusion: The clinical team leader and I concur with Dr. Ehrlich's conclusions on the safety of eltrombopag in pediatric patients. The safety profile in pediatric patients in similar to that seen in adult patients. There are no outstanding safety issues that would preclude approval of the NDA submission.

9. Advisory Committee Meeting

There was no Advisory Committee meeting held for this application because the pivotal trials were agreed upon by the Agency and the Applicant in advance of trial conduct due to these trials being under a pediatric written request.

10. Pediatrics

The clinical trials reviewed in this NDA, TRA108062/PETIT and TRA115450/PETIT2, were conducted in response to a Written Request provided by the FDA. The clinical review team was of the opinion that the Applicant met or exceeded all aspects of the Written Request, and the comparison of the Written Request and information provided in the trials is presented in Table 37 of the clinical review. This comparison was based on the final Pediatric Written Request dated November 23, 2011. [*Source, Primary Clinical Review; Section 9.4*]

11. Other Relevant Regulatory Issues

- Application Integrity Policy (AIP): As of August 4, 2015, there were no AIP issues raised during the pre-approval manufacturing inspections for this NDA.

- Exclusivity or patent issues of concern: The Division was notified via email on July 27, 2015 that the Pediatric Exclusivity Board had reviewed the Exclusivity Determination and agrees that Pediatric Exclusivity will be granted. Formal notification of this decision is pending at the date of this review.

- Debarment certification - Debarment certification was submitted by the Applicant in module 1.3.3.

- Financial Disclosures - In compliance with 21 CFR Part 54 Financial Disclosure by Clinical Investigators, GlaxoSmithKline (GSK) provided financial interest information for clinical investigators participating in studies covered by the rule included in this application.

  GlaxoSmithKline (GSK) relied upon investigator financial interest information provided by the investigators through questionnaires based on site specific study start and completion dates. All investigators have supplied information upon commencement of their participation in the study. No investigator had a financial interest in GSK at the start

of his/her participation in the covered study. In addition, no current or former GSK employee was an investigator in the covered studies.

Significant payments of other sorts from the sponsor of the covered study [21 CFR 54.4(a) (3) (ii), 54.2(f)] - No Significant Payments of Other Sorts were reported. Of the 265 investigators who participated in the studies in this submission, 105 were located in the US. 76 of these US investigators have a CID, and were screened through the Aggregate Spend Data Collection (GASDC) system. The following Significant Payments of Other Sorts (SPOOS) was found:

(b) (6) participated in study (b) (6) over a three year period. GSK discovered $91,377.48 in unreported Grants to Fund Ongoing Research.

Complete List of SPOOS by Study:

(b) (6)

(b) (6) was a Principal Investigator for center (b) (6) which recruited (b) (6) subjects from a total of (b) (6) Subjects, which was (b) (6) % of the total recruitment. The study statisticians were consulted, and an analysis was performed, which determined no impact to the study.

CDTL Conclusion: According to the clinical team, the trial data for PETIT and PETIT2 is considered reliable.

- Other GCP issues: None

- DSI audits: No DSI audit was requested for this NDA. DHP consulted OSI for the clinical site inspections on January 29, 2015, in support of NDA 022291/S-015. Refer to the CDTL review by Virginia E. Kwitkowski, MS, ACNP-BC, DHP Clinical TL for details on the clinical site inspection. According to the CDTL review, the clinical sites were found acceptable.

- Other discipline consults: Yes, the manufacturing facility inspections, PMCs and labeling are pending.

- Any other outstanding regulatory issues: None

12.Labeling

The Applicant proposed changes to the existing Promacta label in the following sections:

- Boxed Warning
- Section 1 - Indications and Usage: Expand the pediatric indication for ages 6-17 to 1 year and older.

- Section 2 - Dosage and Administration
- Section 3 - Dosage Forms and Strengths
- Section 5 – Warning and Precautions
- Section 6 - Adverse Reactions
- Section 7 - Drug Interactions
- Section 8 - Use in Specific Population
- Section 11 – Description
- Section 12 – Clinical Pharmacology
- Section 14 – Clinical Studies
- Section 16 - How Supplied/Storage and Handling
- Section 17 – Patient Counseling Information
- Medication Guide
- Instructions for Use for Promacta (eltrombopag) for oral suspension

All relevant disciplines contributed the labeling. Office of Prescription Drug Promotion (OPDP) did not have any comments to the draft PI**.** Labeling negotiations are ongoing at the time of this review. On July 24, 2015, the Division sent the most recent revisions to the label to the Applicant and they returned the label to us on July 28, 2015; it is currently under review.

The clinical team requested that the following statement be removed from the full prescribing information and instructions for use, (b) (4) (b) (4) This statement was removed since the applicant (b) (4)

Proprietary name: Promacta. The proprietary name has been previously reviewed and found acceptable.

DMEPA comments: In the review dated July 14, 2015, the DMEPA reviewer (Michelle Rutledge, Pharm.D., final signature July 14, 2015) identified several specific deficiencies in Dosage and Administration Section (Section 2) and Patient Counseling (Section 17) of Prescribing Information, and Instructions for Use (IFU). These deficiencies were conveyed to the applicant. Except for the IFU, the applicant submitted revised labeling incorporating the DMEPA's recommendations. DMEPA recommendations were included in the IFU and will be forwarded to the applicant.

Medication guide/Instructions for Use: A medication guide (MG) and IFU was reviewed by the review team. As of the date of this review, the MG and IFU has not been sent to the applicant or reviewed by patient labeling or OPDP.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action: Regular approval pending an approval recommendation from the Office of Process and Facilities and agreed labeling and PMCs.**

The proposed indication for this New Drug Application (NDA 207027) is the following (proposed change to existing indication for PROMACTA shown by underline):

PROMACTA is indicated for the treatment of thrombocytopenia in adult and pediatric patients 1 year and older with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy

- **Risk Benefit Assessment:** All members of the review team agreed that eltrombopag has a favorable benefit to risk profile for pediatric patients aged 1 year and older.

- **Recommendation for Postmarketing Risk Management Activities:** None.

- **Recommendation for other Postmarketing Study Commitments:** The following PMCs are recommended:

    1. Develop a 12.5 mg strength to provide for an additional dosing for patients needing less than the current lowest dose option of 25 mg.

    2. Conduct in-use stability studies using a crushed tablet and the powder for oral suspension in foods or drinks that do not contain polyvalent cations (e.g. applesauce, juice, etc.).

- **Recommended Comments to Applicant**

    No comments are to be conveyed at this time.

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/s/

JANICE T BROWN
08/06/2015