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APPLICATION NUMBER:

207027Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann T. Farrell, M.D.
Subject	Division Director Summary Review
NDA/BLA # Supplement #	207027
Applicant Name	Novartis
Date of Submission	February 24, 2015
PDUFA Goal Date	August 24, 2015
Proprietary Name / Established (USAN) Name	Promacta/eltrombopag olamine
Dosage Forms / Strength	25 mg powder for oral suspension
Proposed Indication(s)	treatment of thrombocytopenia in pediatric patients 1 year and older with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.
Action/Recommended Action for NME:	<i>Approval</i>

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Lori Ehrlich, M.D., Ph.D./Virginia Kwitkowski, MSN, RN, ACNP-BC
Statistical Review	Chia-Wen Ko, Ph.D./Lei Nie, Ph.D.
Pharmacology Toxicology Review	Ramadevi Gudi, Ph.D./Christopher M. Sheth, Ph.D.
CMC Review/OBP Review	N/A
Microbiology Review	N/A
Clinical Pharmacology Review	Jee Eun Lee, Ph.D./Bahru Habtemariam, Pharm.D./Nitin Mehrotra, Ph.D
DDMAC	James Dvorsky
DSI	Anthony Orenca, M.D./Janice Pohlman, M.D./Kassa Ayalew, M.D.
CDTL Review	Virginia Kwitkowski MSN, RN, ACNP-BC

Signatory Authority Review Template

1. Introduction

Promacta is an orally administered thrombopoietin receptor agonist. This submission is for a new formulation which enables product use by younger pediatric patients.

On November 20, 2008, GSK's Promacta (eltrombopag olamine) received initial approval for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Since that original submission, Promacta has received other indications.

On February 24, 2015 GSK submitted this application for a new formulation.

This supplement was given priority review.

2. Background

From the primary reviewer's text for NDA 022291s015:

The incidence of acute ITP in children is 2.5-5.3/100,000 children with the highest incidence rates in 1-7 year old (mean 5.7 years).

- *Chronic ITP is defined as a duration of thrombocytopenia of >6 months. Approximately 15-30% of cases of acute ITP in children become chronic.*
- *The rate of chronic ITP among children is more common in adolescents.*

GSK has submitted a supplement under NDA 022291 s015 containing clinical data for treatment of children with chronic ITP ages 1-17 years. The currently marketed formulation is a tablet for oral administration. This tablet formulation was used for the treatment of children in the older cohorts, ages 6-17 years.

GSK has submitted this NDA (207027) for Promacta, a powder for oral suspension, a pediatric formulation useable for younger children. With approval of NDA 207027, information on all age cohorts specifically those aged 1-5 years, will be made available and incorporated into labeling.

3. CMC/Device

The CDTL memo states the following regarding shelf-life, storage and reconstitution:

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.

The CDTL memo also noted the differences in dietary habits for young children compared with adults. Specifically the concern was that the time window between feedings and calcium contents of diets are different. Therefore a PMC was recommended to study both formulations in soft food.

Also due to the concern that parents of children required 12.5 mg dose may prepare a 25 mg stick pack and instead of discarding the remainder “save” the remainder for the next day’s dose. A second PMC was recommended to create a 12.5 mg stickpack.

4. Nonclinical Pharmacology/Toxicology

No issues arose which would preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The following text is from their review:

Concerning Biopharmaceutics

Although in vitro dissolution data support consistent release from PfOS batches, PfOS and the tablet formulations are not bioequivalent. Administration of eltrombopag PfOS, with a maximum recommended therapeutic dose of 75 mg/day, requires reconstitution with 20 mL water

(b) (4)

Stability of eltrombopag with PfOS has been demonstrated with sample processing and long-term storage. Because PfOS is not bioequivalent to the table formulations, the applicant proposes that platelet counts be monitored weekly for 2 weeks when a patient switches between formulations. Furthermore, 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 C_{max} 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, we 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.

Concerning 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 East 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 $\geq 80\%$ 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.

The review team did not identify any issues which would preclude approval. However based on their analysis they wrote:

We do not agree with the sponsor's proposal [REDACTED] (b) (4)
[REDACTED] 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 is recommended. Our recommendation is intended to simplify the dosing regimen and minimize the number of dose

titration required to achieve target platelet count. Furthermore, the reviewers have concerns on large fluctuation of eltrombopag concentration (b) (4)

The team did recommend a PMC. Below is the text from their review:

1.2 Phase 4 Commitments

We recommend that the applicant develop 12.5 mg strength of the PfOS formulation in order to enable required dose adjustments to achieve target platelet count. Currently available dispensing unit for oral suspension is 25 mg only which is not desirable for adequate dose titration in pediatric patients.

I concur with their recommendation and recommend the labeling reflect their recommendation.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

The primary clinical reviewer reviewed the **PE**diatric patients with **T**hrombocytopenia from **ITP** (PETIT) and PETIT2 trials for efficacy and safety information on use of Promacta to treat pediatric patients with chronic ITP. Per the review:

Key eligibility criteria were patients ages 1 to <18 years, a confirmed diagnosis of chronic ITP for at least 6 months, and a platelet count <30 Gi/L. Subjects were refractory or relapsed after at least one prior ITP therapy, or not eligible, for a medical reason, to continue other ITP treatments. Subjects receiving concomitant ITP medication were allowed to continue with a dose that had been stable for at least 4 weeks prior to Day 1.

The PETIT trial had multiple endpoints including:

Primary Endpoint: The proportion of subjects achieving platelet counts ≥ 50 Gi/L at least once between Days 8 and 43 (Weeks 1 and 6) of the Randomized Period.

Key Secondary Endpoints (during randomized period):

- The proportion of subjects with platelet counts ≥ 50 Gi/L during treatment with eltrombopag in $\geq 60\%$ of assessments between Weeks 2 and 6
- The proportion of patients requiring rescue ITP medications
- The ability to reduce bleeding symptoms.

Key Efficacy Endpoints (during open-label period):

- Proportion of patients achieving platelet counts ≥ 50 Gi/L at any time during the 24 weeks of eltrombopag treatment
- The proportion of subjects that reduced or discontinued baseline concomitant ITP medications
- The proportion of subjects that required protocol-defined rescue treatment
- The ability to reduce bleeding symptoms.

The PETIT2 trial had multiple endpoints including:

Primary Efficacy Endpoint: The proportion of subjects on eltrombopag, compared to placebo, achieving platelet counts ≥ 50 Gi/L for at least 6 out of 8 weeks, between Weeks 5 to 12 of Randomized Period.

Key Secondary Endpoints (during randomized period):

- The proportion of subjects that achieved platelet counts ≥ 50 Gi/L at any time during the first 6 weeks and first 12 weeks
- The proportion of patients requiring rescue ITP medications
- The ability to reduce bleeding symptoms.

Key Efficacy Endpoints (during open-label period):

- Proportion of patients achieving platelet counts ≥ 50 Gi/L at any time during Part 2
- The proportion of subjects that reduced or discontinued baseline concomitant ITP medications
- The proportion of subjects that required protocol-defined rescue treatment
- The ability to reduce bleeding symptoms.

Both trials enrolled patients appropriate for the condition and need for treatment. The revised primary reviewer's tables below show the combined efficacy analysis for the PETIT Trials.

Patients with a platelet response at least once in the first 6 weeks of the randomized period (Combined Analysis)

Age Cohort	Eltrombopag	Placebo
Overall	68/108 (63.0%)	12/51 (23.5%)
Cohort 1 (12-17 years)	26/40 (65.0%)	2/18 (11.1%)
Cohort 2 (6-11 years)	29/44 (65.9%)	6/22 (27.3%)
Cohort 3 (1-5 years)	13/24 (54.2%)	4/11 (36.4%)

Patients with a sustained platelet response (Combined Analysis)

Age Cohort	Eltrombopag	Placebo
Overall	42/108 (38.9%)	1/51 (2.0%)
Cohort 1 (12-17 years)	16/40 (40.0%)	1/18 (5.6%)
Cohort 2 (6-11 years)	18/44 (40.9%)	0/22 (0%)
Cohort 3 (1-5 years)	8/24 (33.3%)	0/11 (0%)

Based on these and other analyses, the primary clinical reviewer stated in the review:

Regular approval is recommended for eltrombopag for the treatment of

thrombocytopenia in pediatric patients ≥1 years old with chronic idiopathic thrombocytopenia (ITP) who have 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.*

The rationale for this recommendation is based on the following information:

- The efficacy of the proposed therapy in terms of increasing platelet counts in pediatric patients with ITP is supported by the pivotal studies TRA108062 and TRA115450. The studies were randomized, double-blind, placebo-controlled, multicenter, multinational trials. These trials provide substantial evidence of effectiveness as the evidence is from adequate and well-controlled trials.*
- Both trials also showed favorable efficacy in clinically relevant endpoints including the reduced need for rescue medications or platelet transfusions and the reduction in baseline ITP medications.*
- The pivotal trials failed to show efficacy in terms of a reduction or prevention of overall bleeding in patients with ITP. However, the trials did show a reduction in clinically significant bleeding defined as Grade 2 to 4 on the WHO Bleeding Scale.*

I concur with the clinical and statistical review teams that this new formulation should be approved based on the data submitted.

8. Safety

The primary reviewer stated that:

- The safety profile in pediatric patients is similar to that seen in adult patients. The common AEs that occurred more frequently in patients treated with eltrombopag than patients treated with placebo were upper respiratory tract*

infection, nasopharyngitis, cough, diarrhea, rhinitis, abdominal pain, oropharyngeal pain, toothache, rash, AST increased, and rhinorrhea. These AEs tended to be low grade, and SAEs were uncommon. There were no deaths in either pediatric trial, and evaluation of AEs of special interest did not reveal any safety signal in pediatric patients treated with eltrombopag. The safety monitoring was appropriate and acceptable to identify the important safety concerns.

- *Other AEs of special interest with the adult eltrombopag experience including hepatotoxicity, cataracts, thromboembolic events and bone marrow toxicity did not occur in pediatric patients receiving eltrombopag in the trials reviewed. This adverse reaction is a warning and precautions in the current Promacta labeling. More thromboembolic events were noted in the eltrombopag arms than the placebo arms of the trials.*

I concur with the recommendations.

9. Advisory Committee Meeting

No issues arose requiring an advisory committee meeting

10. Pediatrics

This application and sNDA 022291 contain pediatric data to allow for labeling of a pediatric indication. This application and the most recent supplement for NDA 022291 will fulfill a pediatric written request.

11. Other Relevant Regulatory Issues

The Office of Scientific Investigation did not find the data unreliable based on their inspection. SEALD reviewed and concluded:

The review concludes that the evidence submitted by the sponsor is inadequate to demonstrate that the Kids' ITP Tools (KIT) is not adequate to measure health related quality of life in children with chronic idiopathic thrombocytopenia.

12. Labeling

The discipline specific teams all participated in labeling negotiations.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action
Regular approval for this indication
- Risk Benefit Assessment

The combined PETIT and PETIT2 trial analysis demonstrated the sustained improvement in platelet counts with eltrombopag added to standard of care

for the pediatric patients with chronic ITP without many available options. Also one of the combined analyses suggested a reduction in any bleeds and clinically significant bleeds. The safety profile was similar for pediatric patients compared with adult patients except that certain AEs of special interest seen with the adult experience with eltrombopag such as hepatotoxicity, cataracts, thromboembolic events and bone marrow toxicity did not occur in pediatric patients receiving eltrombopag in the trials reviewed.

- Recommendation for Postmarketing Risk Management Activities
Continue Post-Marketing Surveillance
- Recommendation for other Postmarketing Study Commitments
Two recommended PMCS were generated after review of the data based on various disciplines. Final language will be reflected in the approval letter:

The following text is from the primary clinical reviewer:

- 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.*

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/s/

ANN T FARRELL
08/17/2015