CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207027Orig1s000

PHARMACOLOGY REVIEW(S)

Memorandum

NDA 207027
Drug: PROMACTA (eltrombopag)
Indication: Thrombocytopenia/severe aplastic anemia
Applicant: GlaxoSmithKlline

This memorandum is in reference to the approvability of GSK's PROMACTA for oral suspension (25 mg packet).

A comment was included in the CMC close-out memo for NDA 207027 regarding a genotoxic impurity that appears in the prepared suspension. The impurity (b) (4) was positive for genotoxicity in the presence of a metabolic activation system, using a high throughput screening Ames assay. The Applicant has elected to control the impurity according to the threshold of toxicological concern (TTC), whereby the acceptable intake of a mutagenic impurity of (b) (4) µg per person per day is associated with a negligible lifetime cancer risk.

Conclusions: The issue of the genotoxic impurity (b) (4) that forms after preparation of the PROMACTA for oral suspension product is not a concern from the perspective of pharmacology/toxicology. Furthermore, a strategy to mitigate the risk of being exposed to the genotoxic impurity has been implemented in Section 2.4 of the prescribing information where it is stated to "Administer the oral suspension immediately after preparation. **Discard any suspension not administered within 30 minutes after preparation.**" There are no other nonclinical concerns with regards to this impurity at this time.

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/s/

CHRISTOPHER M SHETH
08/19/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	207027
Supporting document/s:	1
Applicant's letter and	February 24, 2015
CDER stamp date:	February 24, 2015
Product:	PROMACTA (eltrombopag) (b) (4) for Oral Suspension; 25 mg (b) (4)
Indication:	treatment of thrombocytopenia in adult and pediatric patients 1 year and older with chronic immune (idiopathic) thrombocytopenia (ITP)
Applicant:	Novartis
Review Division:	Division of Hematology Oncology Toxicology (for Division of Hematology Products)
Reviewer:	Ramadevi Gudi, PhD
Supervisor/Team Leader:	Christopher M. Sheth, PhD
Division Director:	John Leighton, PhD, DABT Ann Farrell, MD (DHP)
Project Manager:	Kimberly Scott

Disclaimer

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1 Executive Summary

1.1 Introduction

Eltrombopag olamine (in short, eltrombopag) is an orally bioavailable, small molecule, thrombopoietin receptor agonist. Eltrombopag has effects in inducing proliferation and differentiation of megakaryocytes from bone marrow progenitor cells. PROMACTA® (eltrombopag) is currently approved for the treatment of thrombocytopenia in adults and pediatric patients older than 6 years with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Eltrombopag is recommended for use in adult ITP patients at a starting dose of 50 mg/day. The dose may be adjusted to achieve and maintain a platelet count ≥50,000/μL as necessary to reduce the risk for bleeding; however, the dose may not exceed 75 mg/day. The approved dosage strengths are 12.5-, 25-, 50-, 75- and 100-mg tablets.

The current submission is for powder formulation for oral suspension (PfOS) for the treatment of (b) (4) pediatric patients 1 year of age and older with chronic ITP to increase platelet counts and reduce or prevent bleeding. The recommended starting dose of eltrombopag is 25 mg daily for pediatric patients with 1 to 5 year of age. The efficacy and safety characteristics of eltrombopag with PfOS in patients 1 to 5 years old were evaluated in 2 pediatric trials (PETIT, PETIT2) along with older pediatric patients (≥6 years) who received the tablet formulation.

1.3 Recommendations

1.3.1 Approvability

The approvability of the PfOS developed for pediatric patients 1 to 5 years of age will be differed to product quality and clinical teams. No new nonclinical data was submitted in this submission, and there are no pharmacology/toxicology concerns regarding eltrombopag olamine at this time.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

There were no labelling changes proposed to the nonclinical sections or subsections of 8, 12.1, and 13.

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/s/

RAMADEVI GUDI
08/04/2015

CHRISTOPHER M SHETH
08/04/2015