CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207027Orig1s000

CHEMISTRY REVIEW(S)

Overall Manufacturing Inspection Recommendation

Edit Task | Task Actions

Task Summary **Task Details** Issues Updates More

Overview **Facility Inspection - Overall Application Recommendation**

Edit Custom Form

Custom Form
Facility Inspection - Overall Application Recommendation

Facility Inspection - Overall Application Recommendation

Facility Inspection - Overall Application Recommendation
Approve

Facility Inspection - Overall Application Re-evaluation Date
9/30/15

Navigation Links

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http://panorama.fda.gov/task/view?ID=54eebce800023cd5e2e15330a5df87d0&activeTab=content-dashboard__5418eab10003b6cd5f0c5f929c4fa823

Assigned To
Zhong Li
IM - OPF Reviewer
Edit Assignment

This will be done by
May 9, 2015
(103 days ago)

Status
In Progress

Requested by
DARRTS Integration

This task is waiting on
2 Tasks

Last Update: Aug 20, 2015
Submitted On: Feb 26, 2015

Reference Number
4009422

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

OFFICE OF NEW DRUG PRODUCTS
DIVISION I, BRANCH II
CMC CLOSE-OUT MEMO FOR THE DIVISION OF HEMATOLOGY PRODUCTS

Date	19-Aug-15
Applicant:	GlaxoSmithKline LLC
Drug:	Promacta
Subject	NDA 207027
Reviewer	Olen Stephens, Ph.D.

The integrated quality assessment review submitted by the Office of Pharmaceutical Quality was filed into Panorama 31-Jul-15 with a recommendation for approval pending an approval facility recommendation. The Office of Process and Facilities completed a facilities assessment and filed a review stating the manufacturing and testing sites are adequate to support approval of NDA 207-027 (filed into Panorama 17-Aug-15). There are no pending review or facilities issues to prevent approval from a CMC perspective.

The applicant has agreed to two post-marketing commitments (PMC's) generated in light of the pediatric patient population. PMC #1 was agreed upon to develop a 12.5 mg dose strength. In the event a dose reduction or incremental dose adjustment is necessary, there is the potential for caregivers to prepare the 25 mg dose strength and then administer only half the dose, saving the rest for a later administration. The prepared suspension forms a genotoxic impurity (b) (4) that has not been qualified at levels (b) (4) after preparation. PMC #2 will evaluate the in-use stability of the product mixed with soft foods that do not contain polyvalent cations (e.g. applesauce, juice, ect.) to enable better patient compliance in young children. Refer to the PMC's filed into DARRTS 19-Aug-15.

Conclusion: NDA 207-027 is recommended for approval from a CMC perspective. Two post-marketing commitments have been issued and agreed upon with the applicant.

Olen Stephens, Ph.D.
Chemistry Acting Branch Chief, ONDP

Olen Stephens -S
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

OFFICE OF NEW DRUG PRODUCTS
DIVISION I, BRANCH II
ENVIRONMENTAL ASSESSMENT MEMO FOR THE DIVISION OF HEMATOLOGY PRODUCTS

Date	19-Aug-15
Applicant:	GlaxoSmithKline LLC
Drug:	Promacta
Subject	NDA 207027 Environmental Assessment Exemption
Reviewer	Olen Stephens, Ph.D.

NDA 207-027 qualifies for an the categorical exclusion listed in 21 CFR Part 25.31(b). GlaxoSmithKline has reviewed market forecasts, indications, and dosage information, and estimates that this action will not cause the concentration of the drug substance active moiety to be one part per billion (1 ppb) or greater at the point of entry into the aquatic environment. GlaxoSmithKline does not have knowledge of any extraordinary circumstances that might cause this action to have a significant effect on the quality of the human environment.

Conclusion: The exemption from a required environmental assessment is granted.

Olen Stephens, Ph.D.
Chemistry Acting Branch Chief, ONDP

Olen Stephens -S

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date:	August 17, 2015
To:	Administrative File, NDA 207027
From:	Zhong Li, Chemist , CDER/OPQ/OPF/DIA/Branch I
Endorsement:	Zhihao Qiu, Branch Chief, CDER/OPQ/OPF/DIA/Branch I
Subject:	**Addendum to NDA 207027 OPQ Review #1: Final Facility Recommendation**
Applicant:	GlaxoSmithKline LLC
Product/Dosage Form:	Promacta (eltrombopag) for oral suspension
PDUFA Date:	August 24, 2015
NDA:	207027

At the time of finalization of the OPQ review to comply with the GRMP date, the OPF facility recommendation was listed as pending. This addendum provides the final facility recommendation as follows:

ASSESSMENT OF THE FACILITIES

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

Manufacturer(s)

1. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment name	FEI Number	Profile Code & Responsibilities	Initial Risks Identified	Current Status	Final Recommendation
SmithKline Beecham (Cork) Limited	1000170338	CSN – Drug substance manufacture and (b) (4) elease testing, stability testing	Unacceptable profile in FACTS (b) (4)	GMP Surveillance Inspection	Acceptable Based on District Recommendation

Reviewer's Assessment:

Initial Facility Risk assessment:

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
SMITHKLINE BEECHAM L MITED (CORK)	1000170338	CSN	API				(b) (4)	GMP Inspection

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

P.3.1 Manufacturer(s)

2. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment name	FEI Number	Profile Code & Responsibilities	Initial Risks Identified	Current Status	Final Recommendation

Glaxo Operations UK Ltd (trading as Glaxo Wellcome Operations)	3003262904	**POW** – Responsible for Manufacture, packaging, Quality control testing of drug product	New dosage form for the site (b) (4)	PAI	Acceptable Based on PAI & District Recommendation
Glaxo Operations UK Ltd (trading as Glaxo Wellcome Operations)	3002807078	**CTL** – Responsible for Stability testing of annual batches of commercial drug product	Low	GMP Surveillance Inspection	Acceptable Based on PAI & District Recommendation

Reviewer's Assessment:

Initial Facility Risk assessment:

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
GLAXO OPERATIONS UK LIMITED	3003262904	POW	DP Mfg Testing	(b) (4)				PAI

(b) (4)

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(b) (4)

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

Following a review of the application, there are no significant, outstanding manufacturing risks that prevent approval of this application. Based on firm inspectional history and district file review, the manufacturing facilities as listed above for NDA 207027 are found to be acceptable.

Zhong Li, Ph.D.

Chemist, OPQ/OPF/DIA/IABI

Zhong Li -S

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Date: 2015.08.17 15:07:57 -04'00'

Supervisor Comments and Concurrence:

I concur with this Facility Assessment.

Zhihao Peter Qiu, Ph.D.
Branch Chief, OPQ/OPF/DIA/IABI

Zhihao Qiu -S

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QUALITY ASSESSMENT

NDA: Approval, pending an approval facility recommendation

NDA 207027
Review # 1

Drug Name/Dosage Form	Promacta (eltrombopag) for oral suspension
Strength	25 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	GlaxoSmithKline LLC
US agent, if applicable	None

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0000 (1)/Original Submission	February 24, 2015
0005 (6)/Quality/Response to Information Request	April 20, 2015
0006 (7)/Labeling/Container-Carton Draft	May 1, 2015
0007 (8)/Quality/Response to Information Request	May 4, 2015
008 (9)/Quality/Response to Information Request	May 27, 2015
0010 (10)/Quality/Response to Information Request	June 6, 2015
0009 (11)/General Correspondence	June 10, 2015
0011 (12)/Quality/Response to Information Request	June 15, 2015
0014 (14)/Labeling/Package Insert Draft	July 28, 2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Danuta Gromek-Woods	ONDP/Branch 2
Drug Product	Danuta Gromek-Woods	ONDP/Branch 2
Process	Xuhong Li	OPF/Branch 1
Microbiology	Jonathan Swoboda	DMA/Branch 3
Facility	Zhong Li	OPF/DIA/Branch 1
Biopharmaceutics	Banu Zolnik	ONDP/Division of Biopharmaceutics-Branch 1
Business Process Manager	Rabiya Laiq	OMPT/CDER/OPQ/OPRO/ DRBPMI/RBPMBI
Application Technical Lead	Janice Brown	ONDP/Branch 2
Laboratory (OTR)	Arzu Selen	Immediate Office
ORA Lead	Paul Perdue Jr.	OGROP/ORA/OO/OMPTO/ DMPTPO/MDTP
Environmental Assessment (EA)	N/A	N/A

Table of Contents

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type III		(b) (4)	N/A	N/A	None
	Type III			N/A	N/A	None
	Type III			N/A	N/A	None
	Type III			N/A	N/A	None

Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	22291	PROMACTA (eltrombopag) tablets
IND	063293	PROMACTA (eltrombopag) tablets PROMACTA (eltrombopag) powder for oral suspension

3. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	--	--	--	--
Pharmacology/Toxicology	--	--	--	--
CDRH		Approval	12-Jul-2015	Janice Polacek
Clinical	--	--	--	--
Other	--	--	--	--

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 207027 is recommended for approval from a product quality perspective, pending an approval facility recommendation.

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) [See USP Controlled Room Temperature]

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

PMC#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.

PMC#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.

Note: The applicant has not agreed to the PMCs and there may be additional changes by the applicant on the exact language.

II. Summary of Quality Assessments

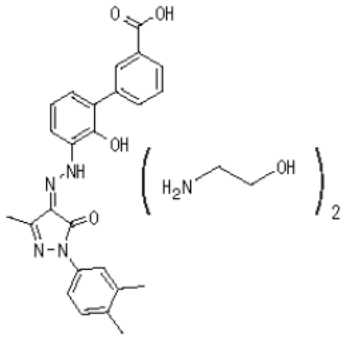
Eltrombopag olamine is currently marketed in the U.S. as Promacta for the treatment of chronic ITP, a low platelet count disorder. The low platelet count disorder occurs in both adult and pediatric populations. The lower strength tablets provide acceptable options for the oldest and mid-range pediatric population. Eltrombopag for oral suspension has been developed for the youngest age group (1-5 year olds) of the pediatric population and patients who cannot swallow tablets. 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 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 (e.g., antacids), calcium-rich foods (e.g., dairy products and calcium-fortified juices), or supplements 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.

Drug Substance, eltrombopag olamine, Quality Summary - CMC information for eltrombopag olamine referenced to the approved marketing application, 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.

Properties, CQAs Relevant to Drug Product Quality - Eltrombopag olamine (3'-{(2Z)-2-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene]hydrazino}-2'-hydroxy-3-biphenylcarboxylic acid - 2-aminoethanol (1:2) has the following structural formula:



Eltrombopag olamine drug substance is [redacted] (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. [redacted] (b) (4) of eltrombopag olamine has been observed to date. [redacted] (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. Eltrombopag olamine is [redacted] (b) (4) as measured by laser diffraction analysis. [redacted] (b) (4) The particle size is a critical quality attribute (CQA) of the drug substance to ensure acceptable drug product performance.

Synthesis – [redacted] (b) (4) Additional information on the synthesis, controls, starting materials, reagents, solvents and auxiliary materials employed in the production of the eltrombopag olamine drug substance along with the release specification is described in NDA 022291.

Impurities - Specified impurities were either qualified in nonclinical studies or do not exceed the ICH Q3A(R2) 0.15% qualification threshold. The specification limits for (b) (4) meet ICH Q3C requirements using the permitted daily exposures and a 75 mg daily dose of drug substance. Therefore, no risk to patients from impurities present in eltrombopag olamine is predicted.

Container Closure - The drug substance is stored in (b) (4)

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

Drug Product, PROMACTA (eltrombopag) for oral suspension (PfOS), Quality Summary

Note: In the NDA, the applicant refers to the drug product name as Promacta (eltrombopag) (b) (4) for oral suspension (PfOS). The drug product 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 executive summary.

Description - 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.

Summary of Product Design - 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. The selection of mannitol was based on knowledge from the commercial eltrombopag tablet product, which also uses mannitol (b) (4)

(b) (4)

(b) (4)

Manufacturing Process – (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).

Container Closure - Eltrombopag PfOS, 25 mg is packaged into heat-sealed foil laminate stickpacks. The laminate material is composed of (b) (4) . The product contact material is the (b) (4) . The laminate was selected to (b) (4)

Shelf life & Storage Conditions - 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) [See USP Controlled Room Temperature].

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].

Co-packaged components – 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 (see figure 1).

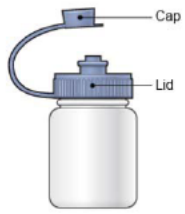
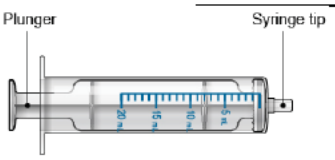
40-cc reconstitution vessel and an Adapta-Cap™ (threaded closure with syringe-port capability) (1 each)	
Reusable oral dosing syringe (1)	

Figure 1: PfOS co-packaged components

Device Review - 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 found the applicant's evaluation of the reconstitution vessel, adapta-cap and oral syringe, acceptable for use.

Office of Testing and Research (OTR) Review – The OTR reviewer recommended the following 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.

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 dosing for 1-2 year olds. Dosing recommendations are included in section 2.4 in the Full Prescribing Information. The Medication Guide 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. The labeling allows administration flexibility either at bedtime or during the day.

  Regarding OTR recommendation #2: Since Promacta is a prescription product, the physician would only prescribe 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."

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 team recommended that a 12.5 mg strength is needed in the event a dose reduction or incremental dose adjustments of 12.5 mg are required (see Executive summary, section Ib, PMC #1).

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 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. As a result, a post marketing commitment 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.) is requested. (see Executive summary, section Ib, PMC #2).

Labeling - Labeling for this NDA is under the Division of Hematology Products pilot program to eliminate numerous labeling meetings for some applications. Once cleared from the team leader, each discipline makes labeling revisions online. After labeling revisions have been made, a single meeting is held with the signatory authority (Ann Farrell, M.D.), CDTL (Janice Brown, M.S.), and Associate Director for Labeling (Virginia Kwitkowski, M., RN, ACNP-BC) to finalize the label. This meeting was held on July 30, 2015 and the label will be sent to consultant reviewers (OPDP and Patient Labeling) for their 2-week review, and then sent to the applicant. The labeling negotiations are ongoing and will be finalized by the Signatory Authority, CDTL, and the Associate Director for Labeling.

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

(b) (4)

(b) (4)

[redacted]

Facility Review –The following facility recommendations are pending as of July 31, 2015.

- **SMITHKLINE BEECHAM LIMITED** (CORK) - CSN NON-STERILE API BY CHEMICAL SYNTHESIS | FEI: 1000170338 | DUNS: 988769360 (6)

  Pending CMS # 87960 and Int'l DO Rec

- **GLAXO OPERATIONS** UK LIMITED - POW POWDERS (INCLUDES ORAL AND TOPICAL) | FEI: 3003262904 | DUNS: 517226676 (6)

  Pending EIR, OPQ GMP & PAI reviews, Int'l DO Rec

- **GLAXO OPERATIONS UK LTD** - CTL CONTROL TESTING LABORATORY | FEI: 3002807078 | DUNS: 228472833 (6)

  Pending EIR and OPQ PAI review

Review Team Recommendation: Approval, pending an approval facility recommendation.

Final Discipline Recommendations

DISCIPLINE	REVIEWER	Recommendation
Drug Substance	Danuta Gromek-Woods	Approval
Drug Product	Danuta Gromek-Woods	Approval
Process	Xuhong Li	Approval
Microbiology	Jonathan Swoboda	Approval
Facility	Zhong Li	Pending
Biopharmaceutics	Banu Zolnik	Approval
Laboratory (OTR) – Product Performance	Arzu Selen	NA, Panorama under Issues tab
CDRH	Janice Polacek	Approval, DARRTS entry on 29-Jul-2015
Application Technical Lead	Janice Brown	Approval, pending an approval facility recommendation

A. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Promacta
Non Proprietary Name of the Drug Product	eltrombopag for oral suspension
Non Proprietary Name of the Drug Substance	eltrombopag
Proposed Indication(s) including Intended Patient Population	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. • Thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. • Patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.
Duration of Treatment	(b) (4)
Maximum Daily Dose	75 mg
Alternative Methods of Administration	None

B. Biopharmaceutics Considerations

1. BCS Classification

The permeability of eltrombopag was determined using MDCK cell line and was categorized as "Moderate". Based on solubility and permeability data, the Applicant classified eltrombopag olamine as a BCS class 2/4 compound (BCS II: low solubility, high permeability; BSC IV: low solubility, low permeability). Therefore, bioavailability of eltrombopag olamine is considered dissolution rate limited.

2. Biostudies

Two pivotal randomized, placebo controlled, multi-center studies were conducted to evaluate the efficacy and safety of eltrombopag in pediatric patients with chronic ITP (study #'s TRA108062 and TRA115450). The Applicant conducted a relative bioavailability study (Study # TRA111718) between eltrombopag for oral suspension, 25 mg, and the approved tablet formulation, 25 mg. Eltrombopag PfOS formulation showed 22% greater bioavailability and 31% higher Cmax than the commercial formulation, therefore dose adjustment may be needed when a patient switches between the for oral suspension formulation to the tablet formulation (for further details refer to the Clinical Pharmacology review).

C. Novel Approaches: None

D. Any Special Product Quality Labeling Recommendations: None

E. Process/Facility Quality Summary (see Attachment A)

F. Life Cycle Knowledge Information (see Attachment B)

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ASSESSMENT OF THE BIOPHARMACEUTICS

Previously NDA 22291, Promacta (eltrombopag) tablets (12.5 mg, 25 mg, 50 mg, 75 mg, 100 mg) was approved on November 20, 2008 for the treatment of thrombocytopenia in patients with chronic immune (idiopatic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy. The proposed drug product is a single use presentation of 25 mg eltrombopag powder for oral suspension. The content of the stickpack is reconstituted with water and is intended to be dosed immediately within 30 minutes of reconstitution.

The results from two pivotal randomized, placebo controlled, multi-center studies (PETIT, # TRA108062 and PETIT 2, # TRA115450), designed to evaluate the efficacy and safety of eltrombopag **pediatric patients** with chronic ITP, formed the clinical basis for approval of this NDA. In the PETIT studies, subjects in the older age cohorts (ages 6-17 years) received eltrombopag tablets, and subjects in youngest age cohorts (ages 1-5 years) received the powder for oral suspension formulation.

13. **Are the in-vitro dissolution test and acceptance criteria adequate for assuring consistent bioavailability of the drug product?**
The dissolution method proposed as a quality control test for eltrombopag powder for oral suspension is summarized below:

USP Apparatus	Rotation Speed	Medium Volume	Temperature	Medium
USP II (paddle)	50 ± 2 rpm	750 ± 8 mL	37 ± 0.5°C	50 mM potassium phosphate in water, pH 6.8 with 0.2% (v/v) polysorbate 80.
Sample is reconstituted in 12 mL 0.1 N HCl and additionally rinsed with 10 mL 0.1 N HCl prior to pouring into the dissolution vessels.				

14. **Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?**

(b) (4)

[redacted]

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(b) (4)

- **Is the proposed dissolution method bio-relevant? What data are available to support this claim?**
  No, the dissolution method is a quality control tool for the proposed drug product.

- **Is the proposed method acceptable? If not, what are the deficiencies?**
  Yes, the method (USP 2, 50 rpm, 750 mL, 50 mM potassium phosphate in water, pH 6.8 with 0.2% (v/v) polysorbate 80) is acceptable.

- **What are the proposed dissolution acceptance criteria for this product?**

Proposed Dissolution Acceptance Criteria for Eltrombopag Powder for Oral Suspension
Q (b) (4)% at 12 min

- **What data are available to support these criteria?**

  The Applicant provided dissolution profiles (mean, and individual values) of the proposed drug product used in the clinical studies shown in the table and figure format below. The Applicant also provided the dissolution profiles of the stability batches in Figures below.

Table 38 Dissolution Profiles for Batches in Clinical Studies TRA108062 and TRA115450

(b) (4)

Figure 5 Dissolution Profiles for Batches in Clinical Studies TRA108062 and TRA115450

(b) (4)

Figure 6 Dissolution Profiles for Primary Stability Batch 122366132

(b) (4)

Figure 7 Dissolution Profiles for Primary Stability Batch 122366135

Figure 8 Dissolution Profiles for Primary Stability Batch 122366136

- **Is the acceptance criterion acceptable? If not, what is the recommended criterion? Is the setting of the dissolution acceptance criterion based on data from clinical and registration batches? If not, is the setting based on BE or IVIVC data?**
  Yes, the acceptance criterion **(Q (b) (4)% at 12 min)** based on the clinical and registration batches **is acceptable.**

- **What are the highlights of the drug product formulation development?**

  The Applicant conducted a relative bioavailability study (# TRA111718) between eltrombopag powder for oral suspension, 25 mg and commercial tablet formulation, 25 mg. Eltrombopag PfOS formulation showed 22% greater bioavailability and 31% higher C_{max} than the commercial formulation, therefore dose adjustment may be needed when a patient switches between the powder for oral suspension formulation and the tablet formulation (for further details refer to OCP review).

Table 14 Relative Bioavailability Assessment: Comparison of Eltrombopag PfOS, 25 mg and Eltrombopag Tablets, 25 mg

Plasma eltrombopag PK Parameter	PfOS vs Tablet GLS Mean Ratio (90% CI)
AUC(0-∞) (μg h/mL)	1.22 (1.08, 1.38)
Cmax (μg h/mL)	1.31 (1.14, 1.50)

- **Are all the strengths evaluated in the pivotal clinical trials? What data are available to support the approval of lower strengths?**

  Only 25 mg strength is submitted for approval in the application.

D.3 DISSOLUTION AND QBD

- **If the application contains QbD elements, is dissolution identified as a CQA for defining design space?**

  The Applicant utilized Failure Modes and Effect Analysis (FMEA) and Design of Experiments (DOEs) approaches and identified dissolution as one of the critical quality attributes.

- **Was dissolution included in the DoE? What raw materials and process variables are identified as having an impact on dissolution? What is the risk assessment been performed to evaluate the criticality of dissolution?**

  Particle size, salt form, and solubility of the drug substance are identified as the high input API attributes impacting dissolution of the drug product. During drug product development (b) (4) From the manufacturing process perspective, (b) (4) Drug product manufacturing and drug product control strategies are evaluated by the other disciplines in this review.

- **What biopharmaceutics information is available to support the clinical relevance of the proposed design space?**
  N/A
- **Is there any dissolution model information submitted as part of QbD implementation? What is the regulatory application of the dissolution model in the submission? What data are provided to support the acceptability of the dissolution model?**
  N/A

Reviewer's Assessment:

The Applicant's proposed dissolution method and acceptance criterion have been assessed and found acceptable for routine batch release and stability testing:

USP Apparatus	Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criterion
USP II (paddle)	50 ± 2 rpm	750 ± 8 mL	37 ± 0.5°C	50 mM potassium phosphate in water, pH 6.8 with 0.2% (v/v) polysorbate 80.	Q = (b) (4)% at 12 min.
Sample is reconstituted in 12 mL 0.1 N HCl and additionally rinsed with 10 mL 0.1 N HCl prior to pouring into the dissolution vessels.					

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 (b) (4) which in turn minimizes the variability in the dissolution profiles.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:

The Division of Biopharmaceutics has reviewed NDA 207027 for Eltrombopag Powder or Suspension, 25 mg, and found the biopharmaceutics data/information acceptable. From the Biopharmaceutics perspective, NDA 207027 is recommended for **APPROVAL.**

Banu Zolnik, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Supervisor Comments and Concurrence:

I concur with Dr. Zolnik's assessment and approval recommendation for NDA 207027.

Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

ASSESSMENT OF MICROBIOLOGY

15. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Drug Product Specifications
A microbial enumeration test is performed per USP. The drug product specification for total aerobic microbial count is (b) (4) CFU/g and the total yeasts/molds count is (b) (4) CFU/g.
Note to reviewer: (b) (4) has been measured and was determined to be (b) (4) for the stability batches at zero and 12 months. (b) (4) is not a specification, but the applicant anticipates the use of this information to support reduced microbial testing, which is acceptable. The stability data and proposed microbial controls should be reviewed and evaluated at such time as the applicant requests reduced microbial release testing.

Information request dated Apr. 13, 2015:

1. ***Confirm that the microbial enumeration test has been validated per USP<61>.***

2. ***Provide a justification for not including a microbial enumeration test (MET) specification to include the absence of* Escherichia coli *as recommended in USP<1111> for non-aqueous preparations for oral use. If the absence of* E. coli *is added to the MET specification, verify that that the method used to determine the absence of* E. coli *has been verified per USP<62>.***

Summary of responses received in the May 4, 2015 submission: The microbial enumeration test was validated per USP<61>. The final recovery method uses a (b) (4) polysorbate 20. Suitability of recovery for *E. coli* was performed per USP<62>. However, (b) (4) (b) (4) did not demonstrate recovery of *E. coli.* The antimicrobial activity present in the subject drug product does not support the growth of *E. coli*. Thus, the selective test for *E. coli* was not included in the specification as this organism is unlikely to be present in the final drug product.

Stability Summary and Conclusion
The applicant is requesting a twenty-four month expiry. The shelf life specification for microbial enumeration is the same as outlined above for release of the drug product and microbial testing is performed annually. The applicant

has provided stability data for three batches manufactured using the commercial process (batch numbers 122366132, 122366135, and 122366136). These studies are carried out under long-term (30°C/65% RH) and accelerated (40°C/75% RH) conditions. Results are provided for up to one year for long-term conditions and six months for accelerated conditions. Microbial enumeration results at one year were (b) (4) CFU/g, complying with the specification. Three additional batches (batch number R689806, R689808, and R689817), using the proposed commercial manufacturing process, are currently under stability studies. However, results were not provided.

Post-Approval Stability Protocol and Stability Commitment
The applicant commits to performing post-approval stability studies under long-term conditions (25 ± 2°C/60 ± 5% RH) on the first three commercial production lots. Yearly thereafter, at least one production batch is placed on the stability program (Module 2; pages 75 – 76 of 95; "drug-product.pdf;" Submission date: Feb. 24, 2015).

Package Insert
The storage condition is 25°C with excursions permitted to 15 – 30°C. The draft package insert contains instructions and dosing information for both the subject drug product (non-sterile powder for oral suspension) as well as the previously approved tablet form (subject of NDA 022291). The minimum dose indicated in the package is 12.5 mg up to a maximum daily dose of 75 mg. The reconstitution instructions states that the entire content of the stick pack (25 mg) is poured into 20 mL of drinking water and administered orally.

The package insert states that the liquid suspension prepared from the subject drug product should be used immediately, but within 30 minutes. Furthermore, the package insert states that this liquid suspension should be discarded after 30 minutes and any remaining liquid suspension should be discarded. Given the hold time of 30 minutes for the liquid suspension, reconstitution stability studies are not necessary.

Reviewer's Assessment:

The applicant includes microbial release testing in accordance 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.

Adequate

2.3.P.6 Reference Standards or Materials

16. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Dye intrusion confirms the package integrity of the stick pack container-closure. Stick packs were submerged in methylene blue (b) (4) No dye penetration was observed. Results are not provided; however, a narrative describing the results is found on page 2 of 4 ("pharmaceutical-development-p24.pdf;" Submission date: Feb. 24, 2015). Results from a positive control are not described. Since the drug product is a non-sterile powder for oral suspension, patient risk is minimal. No additional information is requested.

Reviewer's Assessment:

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.

Adequate

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

17. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response: The subject drug product does not contain materials of biological origin or derived from biological sources.

Reviewer's Assessment:

Adequate

18. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of

the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: The subject drug product does not contain materials of biological origin or derived from biological sources.

Reviewer's Assessment:

Adequate

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:
The Division of Microbiology Assessment has reviewed NDA 207027 for Eltrombopag Powder or Suspension, 25 mg, and found the microbiology information acceptable. From a microbiology perspective, NDA 207027 is recommended for **APPROVAL.**
Jonathan G. Swoboda, PhD
Microbiology Reviewer
OPQ/OPF/Division of Microbiology Assessment Branch 3

Supervisor Comments and Concurrence:
I concur with the microbiology assessment. NDA 207027 is recommended for **APPROVAL.**
Jessica G. Cole, PhD
Quality Assessment Lead (Acting)
OPQ/OPF/Division of Microbiology Assessment Branch 3

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

The document is under review.

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: Promacta Established Name: eltrombopag	Adequate
Dosage form, route of administration	Dosage: powder Route: for oral suspension	Adequate
Controlled drug substance symbol (if applicable)	NA	
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths		25 mg, powder for reconstitution

Conclusion: Adequate.

(b) "Full Prescribing Information" Section

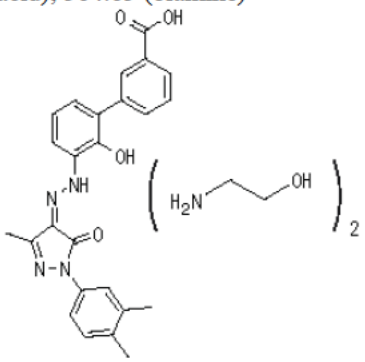
 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Powder for oral suspension	Adequate
Strengths: in metric system	25 mg	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Each packet contains a reddish-brown to yellow powder for reconstitution which delivers eltrombopag olamine equivalent to 25 mg of eltrombopag free acid.	Adequate

Conclusion: Adequate.

#11: Description (21CFR 201.57(c)(12))

PROMACTA (eltrombopag) powder for oral suspension packets contain a reddish-brown to yellow powder which produces a reddish-brown suspension when reconstituted with water. Each 25-mg packet delivers eltrombopag olamine equivalent to 25 mg of eltrombopag free acid.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	PROMACTA (eltrombopag)	Adequate
Dosage form and route of administration	powder for oral suspension	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	25 mg of eltrombopag free acid	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	NA	Adequate
Statement of being sterile (if applicable)	NA	Adequate
Pharmacological/ therapeutic class	A small molecule thrombopoietin (TPO) receptor agonist	Adequate
Chemical name, structural formula, molecular weight	3'-{(2Z)-2-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene]hydrazino}-2'-hydroxy-3-biphenylcarboxylic acid - 2-aminoethanol (1:2) Molecular weight: 442.5 (free acid), 564.65 (olamine) 	Adequate
If radioactive, statement of important nuclear characteristics.	NA	Adequate
Other important chemical or physical properties (such as pKa, solubility, or pH)	Eltrombopag free acid is poorly soluble in water (b) (4) (b) (4) (b) (4) Eltrombopag has three calculate Ka's: pKa1 at (b) (4) pKa2 at (b) (4) and pKa3 at (b) (4)	Adequate

Conclusion: Adequate.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

The 25-mg powder for oral suspension is a reddish-brown to yellow powder in unit-dose packets, co-packaged in a kit with a 40-cc reconstitution vessel, an oral dosing syringe, and a threaded closure with syringe-port capability.

Each kit (NDC 0007-4515-27) contains 30 packets: NDC 0007-4515-01.

Store at room temperature between 20°C and 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Following reconstitution, the product should be administered immediately but may be stored for a maximum period of 30 minutes between 20°C and 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	25 mg as eltrombopag free acid	Adequate
Available units (e.g., bottles of 100 tablets)	Each kit contains 30 packets	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Powder for oral suspension is a reddish-brown to yellow powder in unit-dose packets, co-packaged in a kit with a 40-cc reconstitution vessel, an oral dosing syringe, and a threaded closure with syringe-port capability. Each kit (NDC 0007-4515-27) contains 30 packets: NDC 0007-4515-01.	Adequate
Special handling (e.g., protect from light, do not freeze)	Following reconstitution, the product should be administered immediately but may be stored for a maximum period of 30 minutes between 20°C and 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].	Adequate
Storage conditions	Store at room temperature between 20°C and 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].	Adequate

Manufacturer/distributor name listed at the end of PI, following Section #17

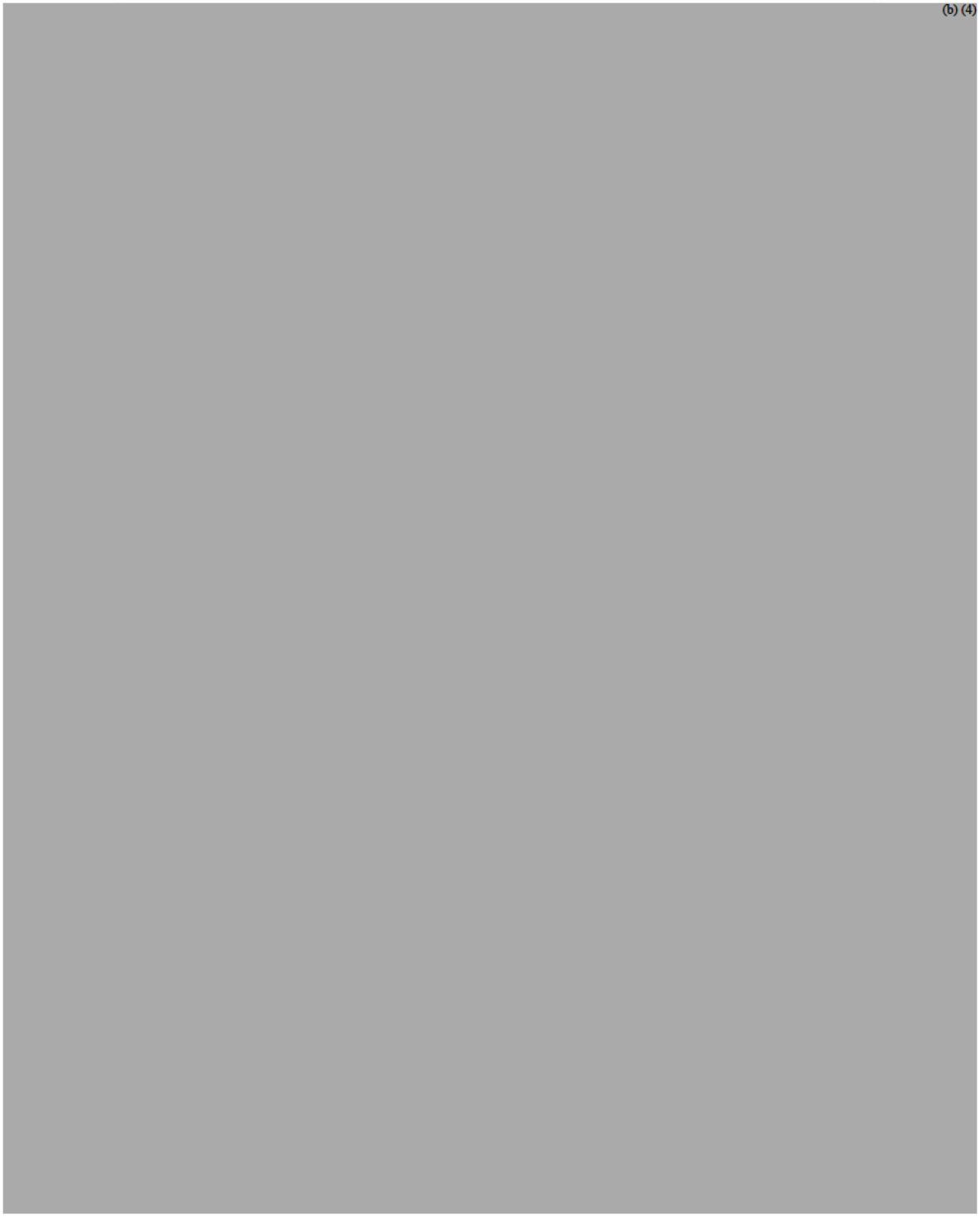
Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	GlaxoSmithKline Research Triangle Park, NC 27709	Adequate,

Conclusion: Adequate.

2. Container and Carton Labeling

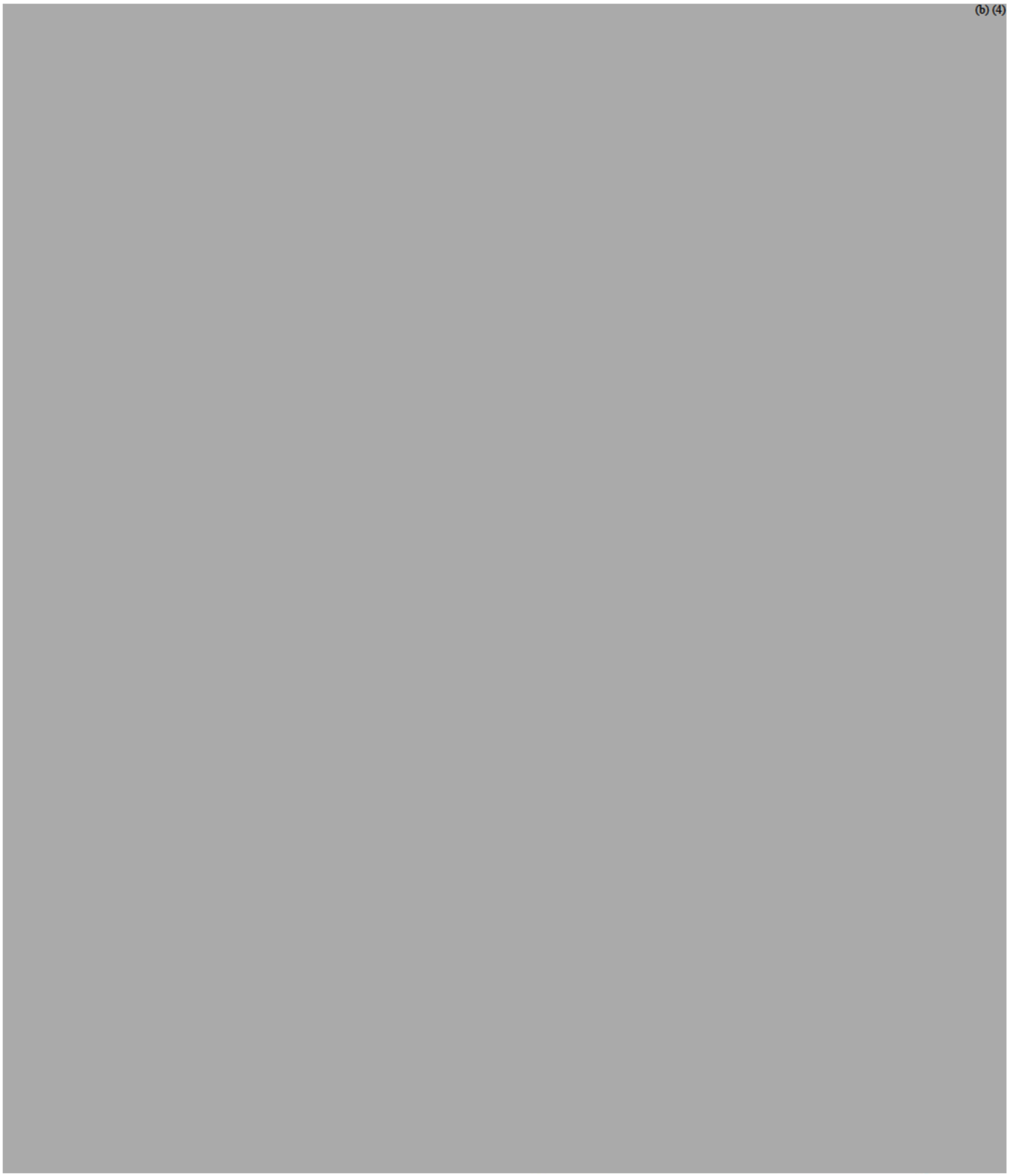
1) Immediate Container Label

(b) (4)



4) Draft Inner Carton

(b) (4)



Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	PROMACTA (eltombopag)	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	25 mg as eltrombopag free acid	Adequate
Net contents (21 CFR 201.51(a))	30 packets of powder for oral suspension	Adequate
Lot number per 21 CFR 201.18	Provided.	Adequate.
Expiration date per 21 CFR 201.17	Provided.	Adequate.
"Rx only" statement per 21 CFR 201.100(b)(1)	Provided.	Adequate.
Storage (not required)	Provided.	Adequate.
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided.	Adequate.
Bar Code per 21 CFR 201.25(c)(2)**	Provided.	Adequate.
Name of manufacturer/distributor	Glaxo SmithKline	Adequate.
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Adequate.

5) Outer Carton

(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	PROMACTA (eltombopag)	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	25 mg as eltrombopag free acid	Adequate
Net contents (21 CFR 201.51(a))	30 packets of powder for oral suspension	Adequate
Lot number per 21 CFR 201.18	Provided.	Adequate.
Expiration date per 21 CFR 201.17	Provided.	Adequate.
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	Provided.	Adequate.
Sterility Information (if applicable)	Provided.	Adequate.
"Rx only" statement per 21 CFR 201.100(b)(1)	Provided.	Adequate.
Storage Conditions	Provided.	Adequate.
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Glaxo SmithKline	Adequate.
Bar Code per 21 CFR 201.25(c)(2)**	PROMACTA (eltombopag)	Adequate
Name of manufacturer/distributor	25 mg as eltrombopag free acid	Adequate
"See package insert for dosage information" (21 CFR 201.55)	30 packets of powder for oral suspension	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	Provided.	Adequate.
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	Provided.	Adequate.

Conclusion: Adequate.

II. List of Deficiencies To Be Communicated

A. Drug Substance – See discipline specific review section for deficiencies, if any.
B. Drug Product – See discipline specific review section for deficiencies, if any.
C. Process/Facility – See discipline specific review section for deficiencies, if any.
D. Biopharmaceutics – See discipline specific review section for deficiencies, if any.
E. Microbiology – See discipline specific review section for deficiencies, if any.
F. Label/Labeling - Ongoing

III. Attachments

A. Facility

OVERALL RECOMMENDATION:				
DRUG SUBSTANCE				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION
DRUG PRODUCT				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION

B. Lifecycle Knowledge Management

a) Drug Substance - NA

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Initial Risk Ranking*	Justification	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments**
	H, M, or L			Acceptable or Not Acceptable	

b) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments**
Assay, stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	Suitable analytical methodology, suitable container closure and storage conditions	Acceptable	
Physical stability (phase separation)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	The physical stability of the drug product after reconstitution is not applicable since the entire contents of the bottle (b) (4) (b) (4)	Acceptable	
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment	L	Drug substance (b) (4)	Acceptable	

	• Site				
Dosing accuracy	• Dosing device • Formulation • Process Parameters • Scale/equipment • Site	M	Proper kit and reconstitution instructions.	Acceptable	
Palatability	• Formulation • Excipient change • Process parameters • Scale/equipment • Site	M	Suitable formulation design.	Acceptable	
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	Suitable microbial release testing.	Acceptable	
Leachables	• Formulation • Container closure • Process parameters • Scale/equipment • Site	M		Acceptable	
Dissolution (for Suspension only)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	Meeting the acceptance criterion of the approved dissolution test	Acceptable	

*Risk ranking applies to product attribute/CQA
**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

Administrative

A. Application Technical Lead Signature

Digitally signed by Janice T. Brown -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300101685, cn=Janice T. Brown -A
Date: 2015.07.31 09:28:50 -04'00'

B. Endorsement Block

Reviewer Name/Date: See discipline specific review
Secondary Reviewer Name/Date: See discipline specific review
Project Manager Name/Date: Rabiya Laiq.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Office of Testing and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: July 14, 2015

To: Janice Brown, Ph.D., OMPT/CDER/OPQ/ONDP/DNDPI/NDPBII

From: Arzu Selen, Ph.D. Office of Testing and Research

Arzu Selen -S Dig tally signed by Arzu Selen -S DN c=US o=U S Government ou=HHS ou=FDA ou=People cn=Arzu Selen -S 0 9 2342 19200300 100 1 1=1300130359 Date 2015 07 14 12 47 25 04'00'

Through: Lucinda Buhse, PhD, Director, Office of Testing and Research

Lucinda F. Buhse -S Digitally signed by Lucinda F Buhse -S DN: c=US o=U S Government ou=HHS ou=FDA ou=People 0 9 2342 19200300 100 1 1=1300167152 cn=Lucinda F Buhse -S Date: 2015 07 28 11:17:32 04'00'

Subject: **NDA 207027 Eltrombopag olamine (PROMACTA) (b) (4) for Oral Suspension**

The following review focuses on possible issues related to delivery/availability of eltrombopag from the dosage form:

1) Reliability of estimated amount of eltrombopag available for absorption from the PROMACTA Powder for Oral Suspension (PfOS) for the youngest patients (2 years old and younger) and
2) Approach(es) to avoid or minimize potential reduction in eltrombopag exposure in the case of patients who are switched to PROMACTA tablets from the eltrombopag PfOS

Background and introduction

Eltrombopag is a thrombopoietin receptor agonist and proposed for treatment of thrombocytopenia in children with chronic immune (idiopathic) thrombocytopenia (ITP) who have had insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Eltrombopag PfOS was studied in 31 non-East Asian and 7 East Asian pediatric patients aged one to five years old with starting doses of 25-mg once a day (b) (4)

A tablet dosage form of PROMACTA (eltrombopag) was approved in November 2008 (NDA 022291) for adult and pediatric patients 6 years old and older with ITP. In the PROMACTA tablet product labeling, under Dosage and Administration, it states that Promacta tablets should be taken on an empty stomach (1 hour before or 2 hours after a meal). It is also stated that Promacta should not be taken within 4 hours of any medications or products containing polyvalent cations such as antacids, calcium-rich foods and mineral supplements. It is important to note that the labeling for Promacta tablets do not state how the tablets should be taken or given by the caregiver to a pediatric patient. If it is to be taken with a liquid, the liquid and the volume of the liquid are not provided. The Medication Guide does not provide additional information, it states, "Take PROMACTA exactly as your healthcare provider tells you to take it." It is this reviewer's concern that this may be interpreted as acceptable administration of the Promacta tablets with soft foods and/or liquids other than water. Considering the

chelation and food effect (reduced exposure) noted with eltrombopag, mixing crushed eltrombopag tablets into soft foods and liquids can lead to reduced and unreliable eltrombopag exposures in all pediatric patients, particularly, for the two year old and younger patients for the reasons that are discussed in this review.

In the draft labeling (currently under review) for PROMACTA (eltrombopag) tablet and PfOS, it is recommended that eltrombopag powder should be reconstituted only with water (20 mL) (b) (4)
The suspension is intended to be dosed immediately within 30 min of preparation.

Similar to the tablet, chelation of eltrombopag with polyvalent cations is also reported for the eltrombopag powder formulation although it is stated in the submission (NDA 207027) (b) (4)

The combined (tablet and suspension) draft label provides a time window for taking PROMACTA to avoid food effect (i.e. reduced exposure when given with food) and chelation of eltrombopag with medications, calcium rich foods and supplements containing polyvalent cations such as iron, calcium, aluminum, magnesium, selenium and zinc. It states. “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.”

Issues Considered Key for this Review

1. **Likely unreliable and reduced eltrombopag exposure in pediatric patients (particularly, 2 years old and younger)**

   Dosing recommendations, in addition to drug substance and drug product considerations, should also consider the drug product and the patient interface, including feeding patterns, habits, diet, food intake, gastric emptying, and physiology of the pediatric patients.

   Even with the known chelation potential, due to the diet and feeding patterns of this patient population, reduced and variable exposure of eltrombopag would be highly likely such that the patient benefit of eltrombopag may be questionable for infants. In infants, unlike adults, intestinal motor activity is less frequent, and displays irregular peristaltic activity such that chelation with milk and formula containing calcium and other polyvalent cations may be a bigger concern in pediatric patients than in adults. Factors influencing intestinal peristalsis including food intake, feeding habits and diet in infants have been extensively published (1-7).

   Considering that chelation of eltrombopag with polyvalent metal cations is significant for the proposed eltrombopag PfOS, based on adult studies, the effect of chelation and reduction in eltrombopag exposure is a greater concern in young pediatric patients and will be difficult to estimate based on observations from the adult studies. In TRA111718 CSR, following administration of a single 25 mg dose of the eltrombopag PfOS to 40 healthy adult subjects, it was shown that plasma eltrombopag exposure compared to fasting was remarkably (approximately 75%) reduced when given with a high calcium meal (approximately 448 mg calcium, 372 kcal, and 9.1 g fat).

The following table summarizes the effect of high-calcium meal on eltrombopag exposure in healthy adults following administration of the eltrombopag PfOS.

Reduction in eltrombopag exposure, geometric mean ratio (90% CI)

Time of dosing	Reduction in Cmax	Reduction in AUC(0-inf)
With a high calcium meal	79% (76%, 82%)	75% (71%, 88%)
2 hours after a high-calcium meal	48% (40%, 54%)	47% (40%, 53%)
2 hours before a high-calcium meal	14% (2%, 25%)	20% (9%, 29%)

It is also stated in NDA 207027 that the tablet formulation (Study 497115/005) compared against the PfOS demonstrated significantly greater chelation interactions with polyvalent metal cation-containing antacids and high-calcium meals, such that for PROMACTA tablets, approved product labeling recommends administering the PROMACTA tablets at least 4 hours apart from polyvalent metal cation-containing products.

2.Reduced and unreliable eltrombopag exposure if patients on eltrombopag PfOS are switched to PROMACTA Tablet dosage form

In the labeling for the PROMACTA tablets, and also in the combined labeling for the tablets and the PfOS (currently under review), it is stated that the PfOS should be administered with water only while there is no information on how the tablets should be administered as discussed above, and may be currently under discussion by the review team.

It is likely that using the tablets instead of the PfOS may be perceived more convenient by the caregiver, particularly for the 12.5 mg dose and even for higher strengths and lead to switching from the PfOS to the tablet. When patients may not be able to swallow tablets, it is not uncommon to administer tablets crushed in soft foods (such as applesauce, pudding or yogurt) or in liquids such as milk, infant formula and possibly fruit juices. It would be important to inform the caregiver and the patients under what circumstances switching between the two dosage forms is acceptable, if it may be acceptable for eltrombopag.

Caregivers, in the absence of dosing information for selecting suitable vehicles, may switch from the PfOS to tablets for convenience, and as a result, unknowingly compound the problem of switching to a bioinequivalent dosage form with an additional reduction in eltrombopag exposure due to manipulation of the tablet and its administration with an unsuitable soft food and/or a liquid.

Recommendations

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.

Potential Assessments Supporting the Above Recommendations:

1) (b) (4)

2) Determine whether there may be acceptable soft foods and liquids (based on compatibility assessments) (b) (4)

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