CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207027Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

Product Quality Microbiology Review

July 1, 2015

NDA: 207027

Drug Product Name
Proprietary: Promacta
Non-proprietary: Eltrombopag

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
24 FEB 2015	24 FEB 2015	05 MAR 2015	10 MAR 2015
04 MAY 2015	04 MAY 2015	Not applicable	Not applicable

Applicant/Sponsor
Name: Novartis Pharmaceuticals Corporation
Address: One Health Plaza
East Hanover, NJ 07936

Representative: Shanthi Ganeshan, PhD
V.P. and U.S. Head of Drug Regulatory Affairs
Telephone: 862-778-2673 **Fax:** 973-781-5217

Name of Reviewer: Jonathan G. Swoboda, PhD, RAC

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** Original NDA

2. **SUBMISSION PROVIDES FOR:** initial marketing of drug product

3. **MANUFACTURING SITE:** Glaxo Operations UK Limited
Priory Street
Ware, Hertsfordshire
United Kingdom SG12 0DJ

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
   - Non-sterile powder for oral suspension
   - 25 mg in a foil stick pack
   - Oral administration after consumer reconstitution in drinking water

5. **METHOD(S) OF STERILIZATION:** Not applicable

6. **PHARMACOLOGICAL CATEGORY:** Treatment of (b) (4) (b) (4) pediatric patients 1 year and older with chronic immune (idiopathic) thrombocytopenia to increase platelet counts and reduce or prevent bleeding

B. **SUPPORTING/RELATED DOCUMENTS:** Not applicable

C. **REMARKS:** This submission is in eCTD format. Only sections related to patient risk associated with a non-sterile powder for oral suspension are reviewed below. Other sections of the review template are deleted, as they are not applicable to this non-sterile product. This submission is a priority-expedited review. The drug product is packaged with a 40 cc reconstitution bottle, a 20 mL oral dosing syringe and a threaded closure with syringe-port capability. These components are of minimal microbiological risk, and therefore, not reviewed below. An information request was sent to the applicant on Apr. 13, 2015 and the responses received in the May 4, 2015 submission are incorporated into the body of this review.

Filename: 0207027.doc

Reference ID: 3813450

Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommended for Approval

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – Not applicable

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – [redacted] (b) (4) produces the non-sterile drug product.

B. Brief Description of Microbiology Deficiencies – Not applicable

C. Assessment of Risk Due to Microbiology Deficiencies – Not applicable

D. Contains Potential Precedent Decision(s) - ☐ **Yes** ☒ **No**

III. Administrative

A. Reviewer's Signature _____
Jonathan G. Swoboda, PhD, RAC

B. Endorsement Block _____
Jessica G. Cole, PhD
Quality Assessment Lead (Acting)

C. CC Block
This review is in Panorama.

Reference ID: 3813450

Product Quality Microbiology Assessment

All of the information in this review relates to patient risk associated with this non-sterile powder for oral suspension.

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

P DRUG PRODUCT DILUENT

P.1 Description of the Composition of the Diluent

- **Description of drug product** – 25 mg of a non-sterile reddish-brown to yellow powder in an elongated stick pack, reconstituted by the consumer in 20 mL of drinking water

- **Drug product composition –**
  Table 1- Composition of Eltrombopag Powder for Oral Suspension (Sponsor Table 1 Module 3.2.P.1)

Component	Quantity mg/stickpack	Function	Reference to Standard
Strength	25		
Eltrombopag olamine[1]	(b) (4)	Active	GlaxoSmithKline[3]
Mannitol		(b) (4)	USP/NF and Ph.Eur.
Sucralose			USP/NF and Ph.Eur.
Xanthan gum			USP/NF and Ph.Eur.
Total weight[4] (mg)	1250	-	-

Note:
1. Eltrombopag olamine is the (b) (4) salt of eltrombopag (free acid).
2. (b) (4) of eltrombopag olamine is equivalent to 25 mg of eltrombopag free acid. The salt factor is (b) (4)
3. An internal GlaxoSmithKline standard is applied for eltrombopag olamine.
4. To allow for delivery of the Eltrombopag PIOS 25 mg dose, (b) (4) of the blend (which includes (b) (4) manufacturing overfill) is filled into each stickpack.

Note to reviewer: The subject drug product (b) (4) composition as approved NDA 022291 [Promacta (eltrombopag) tablets] (approved in Nov. 2008). A microbiology review was not found in DARRTS for this submission.

- **Description of container closure system** – Heat-sealed foil laminate stick packs enclose the subject drug product.

Acceptable

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Container-Closure and Package integrity –**
  Dye intrusion confirms the package integrity of the stick pack container-closure. Stick packs were submerged in methylene blue and (b) (4) (b) (4) (b) (4)

Reference ID: 3813450

[redacted] 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.

- **Preservative Effectiveness** – The non-sterile powdered drug product is for single use and no preservative effectiveness studies are required.
- **Justification for not having a microbial limit specification for a non-sterile drug product** – Not applicable

Acceptable

P.3.3 Description of the Manufacturing Process and Process Controls

[redacted]

- **Environmental monitoring including product bioburden –** Microbiological environmental monitoring is routinely performed within the manufacturing areas to monitor control of water, air, surfaces, and equipment (Module 2; page 41 of 95; "drug-product.pdf;" Submission date: Feb. 24, 2015). Alert and action levels are not provided; however, no additional information is requested due to low patient risk associated with a non-sterile powder for oral suspension.

Acceptable

P.5 Control of Drug Product

P.5.1 Specifications

A microbial enumeration test is performed per USP. The drug product specification for total aerobic microbial count is [redacted] CFU/g and the total yeasts/molds count is [redacted] CFU/g.

Note to reviewer: [redacted] has been measured and was determined to be [redacted] for the stability batches at zero and 12 months. [redacted] 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***

Reference ID: 3813450

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) (b) (4) (b) (4) 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.

Acceptable

P.7 Container Closure System See section P.1.

P.8 Stability

P.8.1 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.

Acceptable

P.8.2 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).

Acceptable

P.8.3 Stability Data – See Section P.8.1.

Reference ID: 3813450

R REGIONAL INFORMATION

R.1 Executed Batch Record

The following executed batch records are included in the subject submission: batch numbers R579759, R580246, and R579767 (See Section 3.2.R).

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. 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.

Acceptable

END

Reference ID: 3813450

Jonathan Swoboda -S

Digitally signed by Jonathan Swoboda -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0013691470, cn=Jonathan Swoboda -S
Date: 2015.07.01 10:56:20 -04'00'

Jessica Cole -S

Digitally signed by Jessica Cole -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jessica Cole -S, 0.9.2342.19200300.100.1.1=2000397920
Date: 2015.07.01 11:12:17 -04'00'

Reference ID: 3813450