

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**NDA 22-291**

**CHEMISTRY REVIEW(S)**



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of New Drug Quality Assessment  
Division of Pre-marketing Assessment and Manufacturing  
Science, Branch V

**CMC Reviewer's Memo**

Date: October 6, 2008  
To: NDA 22-291  
Drug Name: Promacta (eltrombopag) Tablets  
Applicant: GlaxoSmithKline  
Through: Sarah Pope, Ph.D., Acting Branch Chief  
From: Sue-Ching Lin, CMC Reviewer  
Subject: Review of the revised container labels submitted on September 29, 2008

**1. Background**

Please refer to the CMC review dated 7/24/08 in DFS for this NDA. During the review of this NDA, this reviewer has identified labeling issues and conveyed the comments to the applicant in the CMC information request letters dated 4/29/08, 5/13/08, 5/15/08, and 5/28/08. The revised container labels, as submitted in the 5/30/08 amendment, have adequately responded to the CMC comments and were found to be acceptable.

The applicant submitted a Medication Guide on August 8, 2008, in response to the request from the FDA during the July 8, 2008 meeting between GSK and the FDA clinical division, when the Risk Evaluation and Mitigation Strategy (REMS) was discussed.

To comply with the Medication Guide Regulations, the FDA requested via the 9/22/08 e-mail that the sponsor revise the container labels in accordance with 21 CFR 208.24(a)(2)(d). In response, GSK submitted the revised container labels on September 29, 2008.

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/s/

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Sue Ching Lin  
10/7/2008 02:22:35 PM  
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Sarah Pope  
10/8/2008 12:26:17 PM  
CHEMIST  
Concur

**ONDQA Division Director's Memo**  
**NDA 22-291, Promacta (eltrombopag) Tablets**  
**Date: September 11, 2008**

**Introduction**

Promacta (eltrombopag) immediate release, film coated tablets (25 mg and 50 mg, Rx only) is used to treat idiopathic thrombocytopenic purpura (ITP) to increase platelet counts and mitigate bleeding.

**Administrative**

The corresponding IND for this NDA is I63,293. This NDA was submitted 12/18/07. A total of seven amendments were reviewed; the latest received on June 13, 2008 in response to a request for controls on \_\_\_\_\_ genotoxic impurities. b(4)

This NDA was received as a NME (Type 1) NDA for priority (P) review. However, owing to clinical deficiencies, the PDUFA deadline was extended by three months to 9/19/08

The NDA contained a substantial amount of Quality by Design (QbD) information. Therefore the CMC review was conducted as a team effort with the Manufacturing Science Branch.

**The application is recommended for an approval (AP) action from chemistry, manufacturing and controls (CMC) perspective.** Minor CMC labeling comments were forwarded to the OND Project manager on 6/16/08.

There are no CMC Phase-IV post-approval agreements.

**Drug Substance**

The drug substance (eltrombopag olamine; USAN) is a new molecular entity and is the olamine salt of \_\_\_\_\_ eltrombopag. The drug substance is synthetic. A failure modes and effects analysis (FMEA) and risk assessment were carried out on the synthetic process to identify (and thereby prevent) potential failures during production. The design of experiments (DOE) was robust and should lead to improved and consistent quality of the drug substance. For example, using \_\_\_\_\_ studies, the applicant was able to develop appropriate controls to limit the genotoxic impurities \_\_\_\_\_ and \_\_\_\_\_ below the threshold of toxicological concern of 1.5 ug/day. b(4)

The NDA also provides for two comparability protocols which were found to be adequate. One is for an \_\_\_\_\_ b(4)

The second is for the use of

b(4)

### Drug Product

As mentioned previously, the drug substance is a salt; eltrombopag olamine. However, the drug product established name; (eltrombopag) Tablets and the tablet strengths of 25 mg and 50 mg correspond to the neutral species (eltrombopag). This is the preferred nomenclature and strength designation format to be used and is consistent with best practices for OND, OGD, and USP.

Both strengths of the tablets are film coated immediate release type and are made by traditional methods. Using QbD approaches, critical process parameters and critical process controls were identified and proven acceptable ranges (PAR) were established for the manufacturing process.

b(4)

Note that the two strengths are NOT proportionately formulated; that is the 50 mg tablet is NOT simply twice the tablet weight of the 25 mg strength.

b(4)

The 25 mg tablets are orange, round, and biconvex, with "GS NX3" debossed on one side and "25" on the other. The 50 mg tablets are blue, round, and biconvex with "GS UFU" debossed on one side and "50" on the other.

The tablets are packaged as thirty tablets in white bottles with child-resistant closures that include foil induction seal liners. In this container closure system, the recommended approved expiration period is thirty six (36) months when stored at controlled room temperature.

b(4)

Rik Lostritto, Ph.D., Director, ONDQA Division III.

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/s/

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Richard Lostritto  
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CHEMIST



**NDA 22-291**

**Promacta<sup>®</sup> (eltrombopag) Tablets**

**GlaxoSmithKline**

**Sue-Ching Lin (Overall)  
Ying Wang, Ph.D. (Manufacturing Science)**

**Office of New Drug Quality Assessment  
Division of Pre-marketing Assessment and Manufacturing Science**

**Chemistry, Manufacturing, and Controls (CMC)  
Team Review of Original NDA  
For the Division of Medical Imaging and Hematology Products  
(HFD-160)**



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# CMC Review Data Sheet

1. NDA 22-291
2. REVIEW #: 1
3. REVIEW DATE: 16-JUN-2008
4. REVIEWERS:  
 Ying Wang (manufacturing science aspect)  
 Sue-Ching Lin (overall)

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original IND 63,293 submission	28-Sep-2004
Original IND 63,293 CMC review	07-Dec-2004
CMC end-of-phase-2 meeting	10-Mar-2005
Follow-up to the 3/10/05 meeting	05-May-2005
The third end-of-phase-2 CMC meeting	14-Dec-2005
CMC only pre-NDA meeting	12-Jun-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA Submission	18-Dec-2007
Amendment (BC) (starting material specification & additional container information)	03-Mar-2008
Amendment (BC) (impurities, dissolution data, etc.)	20-Mar-2008
Amendment (BZ) (degradants, comparability protocol, dissolution acceptance criteria, container labels)	13-May-2008
Amendment (BZ) (dissolution acceptance criteria, design space, manufacturing process, post-approval site changes, container labels, & analytical procedures)	20-May-2008
Amendment (BZ) (revised container labels)	30-May-2008
Amendment (BC) (process description, etc.)	04-Jun-2008
Amendment (BZ) (updated c-CTD files containing recent response to the FDA IR letters and a revised drug substance specification with a footnote for control of genotoxic impurities.	13-Jun-2008

b(4)



CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: GlaxoSmithKline  
Address: 2301 Renaissance Boulevard  
P.O. Box 61540  
King of Prussia, PA 19406  
Representative: Sandra L. Bihary-Waltz, Director, Regulatory Affairs  
Telephone: (610) 787-3796

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Promacta Tablets
- b) Non-Proprietary Name: eltrombopag tablets (Note: the established name for the drug substance is eltrombopag olamine. But the drug product strengths are based on the equivalent amount of the free acid.)
- c) Code Name/# (ONDQA only): SB-49115-GR (for the drug substance eltrombopag olamine)
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 1
  - Submission Priority: P (Priority Review) (Due date was extended due to major clinical amendments)

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

10. PHARMACOL. CATEGORY: Hematological product (short-term treatment of idiopathic thrombocytopenic purpura (ITP))

11. DOSAGE FORM: tablet

12. STRENGTH/POTENCY: 25 mg & 50 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED:  Rx  OTC

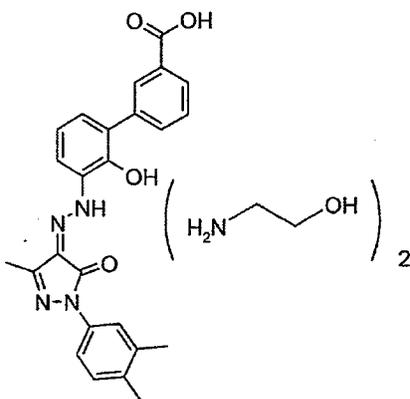
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

## CMC Review Data Sheet

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



IUPAC name:

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)

CAS name:

[1,1'-biphenyl]-3-carboxylic acid, 3'-[2-[(2Z)-1-(3,4-dimethylphenyl)-1,5-dihydro-3-methyl-5-oxo-4H-pyrazol-4-ylidene]hydrazinyl]-2'-hydroxy-, compd. with 2-aminoethanol (1:2)

The CAS Registry Number: 496775-62-3

Molecular formula:  $C_{25}H_{22}N_4O_4 \cdot 2(C_2H_7NO)$ 

Molecular weight for the drug substance: 564.65

Molecular weight for eltrombopag free acid: 442.5

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CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	CODE <sup>1</sup>	STATUS <sup>2</sup>	COMMENTS
-	IV	/	/	10/8/07	4	N/A	See pages 130 & 217*
/	III			5/2/06	4	N/A	See page 231**
/	III			5/3/06	4	N/A	See page 231**
/	III			5/25/07	4	N/A	See page 231**
/	III			4/17/06	4	N/A	See page 231**

b(4)

<sup>1</sup> Action codes for DMF Table:

1 - DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 - Type 1 DMF

3 - Reviewed previously and no revision since last review

4 - Sufficient information in application

5 - Authority to reference not granted

6 - DMF not available

7 - Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	63,293	SB-497115GR

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CMC Review Data Sheet

18. STATUS:

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	5/30/08	Shawnte Adams
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMETS*	The proprietary name "Promacta" is acceptable	5/16/08	Linda Kim-Jung
EA	Categorical exclusion (see review)		Sue-Ching Lin
Microbiology	N/A		

\*DMETS has recently been changed to DMEPA (Division of Medication Error Prevention and Analysis) due to the reorganization.

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Executive Summary Section

# The CMC Review for NDA 22-291

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From the perspective of chemistry, manufacturing, and controls, this NDA is recommended for approval with the understanding that the labeling recommendations made regarding package insert, patient information, and SPL Drug Listing Data Element are considered during the forthcoming labeling meetings.

The CMC reviewers' revisions of the package insert, patient information, and SPL Drug Listing Data Element, which incorporate the comments as shown in the labeling section of this review, have been forwarded to the project manager on June 2, 2008 by e-mail. These labeling revisions will need to be conveyed to the applicant if there is a labeling negotiation between the FDA and the applicant.

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

None

### II. Summary of CMC Assessments

#### A. Description of the Drug Product and Drug Substance

##### (1) Drug Substance

The active ingredient is eltrombopag olamine, which is a new molecular entity. Detailed information regarding the drug substance was provided in the NDA. The established name for the drug substance is "eltrombopag olamine," which is the name in the USAN Dictionary. However, the established name for the drug product should be "eltrombopag tablets," even though the active ingredient is the olamine salt. The reason is that the strengths of the drug product (25 mg and 50 mg) are based on the equivalent amount of eltrombopag free acid in each tablet. According to the current ONDQA Labeling and Nomenclature Committee policy, the established name of the drug product and the declared strength should match.

Executive Summary Section

Substantial amount of Quality by Design (QbD) information has been provided in the NDA. The drug substance is chemically synthesized. An FMEA (Failure Mode and Effects Analysis) risk assessment was used to identify failure modes within the process that may lead to drug substance specification failure. After this assessment, process parameters were then categorized according to whether they were Quality Critical Process Parameters (QCPPs), Quality Process Parameters (QPPs), or Process Parameters (PPs). The applicant states that the QCPPs identified for manufacture of the drug substance are \_\_\_\_\_

b(4)

Design of Experiments (DoE) was performed for each process step, except the intermediate from the contractor. Design space was established for each step. \_\_\_\_\_ studies and extreme conditions were also studies for some steps. Multi-step design space verification was also performed.

Potential and actual impurities arising from the starting materials, the synthetic process, and degradation were identified. Through DEREK computational analysis, five of the potential impurities are identified as having structural alerts for genotoxicity: \_\_\_\_\_ and \_\_\_\_\_. Among these five impurities, \_\_\_\_\_ and \_\_\_\_\_ are genotoxic, based on the Ames test results.

b(4)

The applicant has demonstrated that, using \_\_\_\_\_ studies, controls for the starting materials, in-process controls \_\_\_\_\_, and reactions within design space, genotoxic impurities \_\_\_\_\_, and \_\_\_\_\_ are adequately controlled below the "Threshold of Toxicological Concern" (TTC) of 1.5 µg/day. The controls of regular and genotoxic impurities appear to be acceptable.

b(4)

A QbD approach was applied to some of the analytical procedures for drug substance and drug product. Through DoE studies, method parameters that need to be controlled are identified and proven acceptable ranges are defined.

The NDA proposes two comparability protocols for the post-approval changes in the manufacture of the drug substance: (1) \_\_\_\_\_

\_\_\_\_\_ (2) \_\_\_\_\_  
The proposed filing mechanisms \_\_\_\_\_ are acceptable.

b(4)



Executive Summary Section

commercial manufacturing site. The stability data support the proposed 36-month expiration period for the drug product stored at the proposed controlled room temperature.

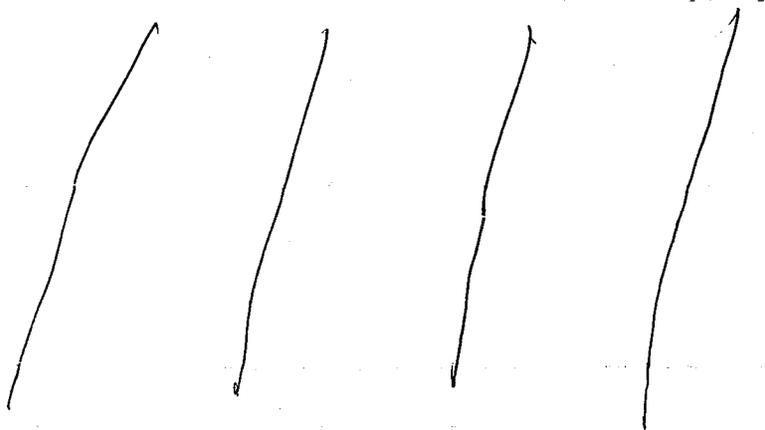
**C. Basis for Approvability or Not-Approval Recommendation**

Detailed pharmaceutical development report and manufacturing process descriptions were provided in the NDA for the drug substance and drug product. Substantial amount of QbD information was provided.

The proposed two comparability protocols for the drug substance manufacture appear to provide improvements to the current process. The filing mechanism for the post-approval changes and the proposed data package, after revisions, are acceptable.

All the analytical procedures have been properly validated. The robustness of some of the analytical procedures for the drug substance and drug product has been demonstrated using multivariate analysis.

The applicant proposed



b(4)

The Office of Compliance has issued an "acceptable" recommendation for each facility used for manufacturing and control of the drug substance and drug product.

The Division of Medication Error Prevention and Analysis (DMEPA), which was recently renamed from DMETS, has no objections to the use of the proposed proprietary name Promacta.

The revised container labels, as amended by the applicant on May 30, 2008, appear to be acceptable. However, other labeling issues (i.e., package insert, patient information, and SPL Drug Listing Data Element) have not been discussed. As indicated earlier, the clinical division has extended the PDUFA due date to September 19, 2008, due to

Executive Summary Section

major clinical submissions. Consequently, labeling issues will not be discussed until the applicant addresses the requested clinical deficiencies. The CMC reviewers' revisions (with track changes) of the package insert, patient information, and SPL Drug Listing Data Element, which incorporate the comments as shown in the labeling section of this review, have been forwarded to the project manager on June 2, 2008 by e-mail. These labeling revisions will need to be conveyed to the applicant if there is a labeling negotiation between the FDA and the applicant.

**III. Administrative**

**A. Reviewer's Signature:**

*(See appended electronic signature page)*

Sue-Ching Lin, M.S., R.Ph., Reviewer, ONDQA  
 Ying Wang, Ph.D, Reviewer, ONDQA

**B. Endorsement Block:**

*(See appended electronic signature page)*

Ravi Harapanhalli, Ph.D., Branch Chief, Branch V, ONDQA

**C. CC Block:** entered electronically in DFS

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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Sue Ching Lin  
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Ying Wang  
7/24/2008 09:16:17 AM  
CHEMIST

Ravi Harapanhalli  
7/24/2008 04:15:38 PM  
CHEMIST

Initial Quality Assessment (IQA)  
Branch V  
Pre-Marketing Assessment and Manufacturing Science Division III  
Office of New Drug Quality Assessment

OND Division: Division of Medical Imaging and Hematology Products  
NDA: 22-291  
Applicant: GlaxoSmithKline  
Stamp Date: 19-Dec-2007  
PDUFA Date: 19-Jun-2008  
Trademark: Promacta Tablets  
Established Name: eltrombopag tablets  
Dosage Form: immediate-release tablet  
Route of Administration: oral  
Indication: short-term treatment of previously-treated patients with chronic idiopathic thrombocytopenic purpura (ITP) to increase platelet counts and reduce or prevent bleeding.

Reviewer: Sue-Ching Lin

ONDQA Fileability: YES  NO   
Comments for 74-Day Letter YES  NO

Summary and Critical Issues:

**A. Summary**

Submission type: The NDA was submitted electronically in CTD format as a 505(b)(1) application. The active ingredient is eltrombopag olamine, a new molecular entity. It has been accepted for priority review. The NDA is a CMC-hybrid submission containing Quality by Design elements as well as traditional information.

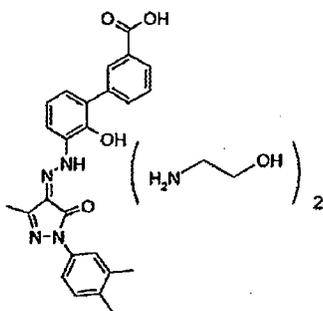
Pre-submission CMC history, issues and/or agreements:

- 9/28/04: Original IND 63,293
- 3/10/05: CMC end-of-phase-2 meeting:
- 5/5/05: Follow-up to the 3/10/05 meeting
- 12/14/05: The third end-of-phase-2 CMC meeting. Discussions include starting materials, genotoxic impurities, drug product specification, stability, etc.
- 6/12/07: CMC only pre-NDA meeting. Discussions include controls of starting materials and intermediates, genotoxic impurities, stability protocol, etc.

Drug Substance:

The established name for the drug substance is "eltrombopag olamine," which is the name in the USAN Dictionary. However, the established name for the drug product should be "eltrombopag tablets," even though the active ingredient is the olamine salt. The reason is that the strengths of the drug product (25 mg and 50 mg) are based on the equivalent amount of eltrombopag free acid in each tablet. According to the current ONDQA Labeling and Nomenclature Committee policy, the established name of the drug product and the declared strength should match.

Eltrombopag olamine has the following chemical structure:



The CAS name is:

[1,1'-biphenyl]-3-carboxylic acid, 3'-[2-[(2Z)-1-(3,4-dimethylphenyl)-1,5-dihydro-3-methyl-5-oxo-4H-pyrazol-4-ylidene]hydrazinyl]-2'-hydroxy-, compd. with 2-aminoethanol (1:2)

The CAS Registry Number is 496775-62-3 and the molecular formula is  $C_{25}H_{22}N_4O_4 \cdot 2(C_2H_7NO)$ .

Eltrombopag olamine is a \_\_\_\_\_

b(4)

The drug substance is chemically synthesized. An FMEA (Failure Mode and Effects Analysis) risk assessment was used to identify failure modes within the process that may lead to drug substance specification failure. After this assessment, process parameters were then categorized according to whether they were Quality Critical Process Parameters (QCPPs), Quality Process Parameters (QPPs), or Process Parameters (PPs). The applicant states that the QCPPs identified for manufacture of the drug substance are \_\_\_\_\_

b(4)

The applicants states that they have identified critical quality attributes (COAs) of eltrombopag olamine as

b(4)

Potential and actual impurities arising from the starting materials and the synthetic route were identified and provided in Section 2.6.6. Forced degradation products of eltrombopag olamine are discussed in Section 7.3. known related substances, have been found in the drug substance and are included in the drug substance specification. Some of the potential impurities in the starting materials, intermediates, and drug substance are structural alerts. Please see the comments below, under the section of "Critical Issues for Review," for issues regarding potential genotoxic impurities.

b(4)

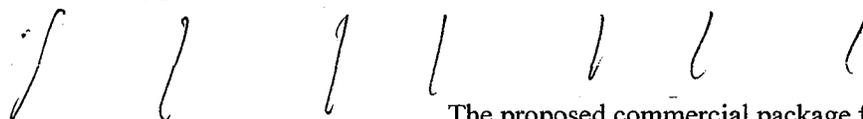
Stability data were provided for the drug substance stored at 30°C/65%RH (24 months) and 40°C/75%RH (6 months) for three primary stability batches. Three months of stability data are provided on three commercial-site specific batches of the drug substance.

Drug Product

The proposed commercial formulation for eltrombopag olamine is an film coated immediate-release tablet. Two strengths are proposed for commercialization, 25 and 50 mg. As noted above in the drug substance section, the strengths of the drug product are based on the equivalent amount of eltrombopag free acid in each tablet. The 25 mg tablets are orange, round, biconvex film coated tablets debossed on one side with an identifying code of 'GS NX3' and '25'. The 50 mg are blue, round, biconvex tablets debossed on one side with an identifying code of 'GS UFU' and '50'.

b(4)

The manufacturing process involves



b(4)

The proposed commercial package for Eltrombopag Tablets, 25 mg and 50 mg is an bottle with a child-resistant closure that includes a faced foil induction seal liner and filled with tablets.

The applicant states that a risk-based approach has been applied throughout the development of eltrombopag drug product to assure that, in addition to meeting the expectations of patients and clinicians, the drug product is capable of meeting appropriate quality standards in routine manufacture at commercial scale. Where appropriate, structured methodologies such as FMEA and BRITEST (Batch Route Innovation Technology Evaluation and Selection Techniques) tools and statistical Design of Experiments (DOE) have been used to identify risk and improve overall product understanding so that appropriate control strategy and risk management can be applied and in line with current regulatory expectations outlined within ICH Q8 and Q9.

Quality critical process parameters and critical process controls are identified and Proven Acceptable Ranges are proposed for the manufacturing process.

It is stated that the stability testing of the 50 mg tablets was performed using a matrix stability protocol as agreed with the agency during discussions at the March 10, 2005 meeting and subsequent facsimile from the FDA on May 5, 2005. Subsequent to this meeting and agreement, a 25 mg tablet was selected for registration in addition to the 50 mg tablet. It was agreed at the End-of-Phase-2 meeting of December 14, 2005 that the stability test protocol for long term storage of the 25 mg tablet would include full testing at each time point.

#### B. Critical Issues for Review

(They are prioritized in order of potential impact on approvability of the NDA. The meeting minutes from the previous meetings with the Agency should be carefully considered while reviewing this NDA. Also, subsequent e-mail correspondence from the applicant regarding the nature and extent of qualification of some genotoxic impurities should be reviewed and discussed with the Pharm/Tox reviewer.)

##### Drug Substance:

1. The reviewers will confirm that the applicant has adequately identified the critical process parameters (QCPPs) and quality process parameters (QPPs) for the drug substance manufacturing.
2. The reviewers will evaluate the acceptability of the submitted FMEA risk assessment.
3. Ensure that \_\_\_\_\_ meets the criteria listed in the December 14, 2005 meeting minutes for a starting material. (Note that FDA has agreed during the 12/14/05 meeting that \_\_\_\_\_ is qualified as a starting material.) b(4)
4. As discussed in the 6/12/07 meeting (questions 4a and 4b), the following potential impurities in the drug substance are structure alerts: \_\_\_\_\_  
\_\_\_\_\_ During the meeting, GSK proposed (slide # 34 of their presentation) to submit batch data — pilot scale and — commercial scale batches) in the NDA to show that these impurities are properly controlled and thus are not required for further testing. The reviewers will evaluate these data to confirm that these potential genotoxic impurities are properly controlled. b(4)
5. Another potential impurity in the drug substance, \_\_\_\_\_ is also a structural alert. The applicant states in section 3.2.S.4.5 (justification of specification) that appropriate in-process controls and results from \_\_\_\_\_ studies have shown that it is not necessary to routinely test this impurity in drug substance. As discussed during the 6/12/07 meeting (question 5), FDA agreed with the sponsor to assess the acceptability of test sunset provision after the manufacture of first — commercial batches. The reviewers will assure sufficient data have been provided to justify for not including this potential genotoxic b(4)

impurity in the drug substance specification and will also take into consideration the above test sunset provision that was earlier agreed to.

6. Review the drug substance specification to see whether the proposed tests in the 6/12/07 meeting (question 6) are included, or justified for their lack of inclusion.
7. \_\_\_\_\_ are impurities that might theoretically be generated during the preparation of SB-797115 (eltrombopag free acid), from \_\_\_\_\_. They have been shown to be genotoxic according to the applicant (section 3.2.S.4.5, under tests not included in the specification). The reviewers will evaluate the submitted data and, based on the maximum daily intake, to assure it is justified not testing for these potential impurities. Also refer to FDA comments to question 7 during the 6/12/07 meeting to see whether additional results on commercial batches are required. b(4)
8. The structures of potential degradants that were formed under forced degradation conditions were provided in the stability section. Ensure the analytical method is capable of detecting potential genotoxic degradants, if any.
9. The applicant proposes \_\_\_\_\_  
\_\_\_\_\_. The reviewers will evaluate the acceptability of the proposal. b(4)
10. The reviewers will evaluate the proposed two comparability protocols for the post-approval changes in the manufacture of the drug substance \_\_\_\_\_  
\_\_\_\_\_. b(4)

Drug Product:

1. Review the pharmaceutical development section for the acceptability of the risk assessment tools and statistical Design of Experiments.
2. Evaluate the acceptability of quality critical process parameters, critical process controls, and design space for the manufacturing process.
3. The applicant proposes to file annual reports for post-approval changes for manufacturing sites and primary packaging sites based on the QbD information submitted in the NDA. The reviewers will evaluate the acceptability of the proposals.
4. The applicant states that the drug substance is classified as a BCS Class 2/4 compound, i.e., at the cusp of BCS Class 2 and 4. The reviewers need to evaluate the dissolution method and acceptance criteria to assure they are suitable for the drug product. Also refer to the FDA response to Question #4 during the 12/14/05 meeting with the sponsor.

5. Evaluate the proposed matrix design for the stability protocol. Refer to the FDA comments in the 3/10/05, 5/5/05, and 12/14/05 meetings.

**C. Comments for 74-Day Letter**

1. Include the test and acceptance criterion for the potential genotoxic impurity \_\_\_\_\_ in the specification for the starting material \_\_\_\_\_, indicating that testing of this impurity will be performed for the first \_\_\_\_\_ batches of the starting material if there is any change in supplier or manufacturing process.

b(4)

2. Provide assurance of safety of all packaging components (in section 3.2.P.7) by reference to appropriate \_\_\_\_\_ regulations. Provide a statement certifying that all packaging components meet the referenced CFR regulations.

b(4)

3. Provide \_\_\_\_\_ testing results for the container closure systems \_\_\_\_\_

b(4)

**NDA FILEABILITY CHECKLIST**

IS THE CMC SECTION OF THE APPLICATION FILABLE? Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	PARAMETER	YES	NO	COMMENTS
1.	Is the CMC section sufficiently complete to permit substantive review to begin?	X		
2.	Is the CMC section indexed, paginated and organized in a manner to allow substantive review to begin?	X		Electronic CTD format
3.	Is the CMC section legible so that substantive review can begin?	X		
4.	Are all of the facilities (manufacturing, packaging, testing, sterilization, etc.) appropriately delineated with full addresses?	X		Attached to Form 356h in module 1
5.	Is a statement provided that all the facilities are ready for cGMP / PAI inspection?	X		Attached to Form 356h in module 1
6.	Has the applicant developed an environmental impact assessment or claimed categorical exclusion under the applicable regulations?	X		A categorical exclusion is claimed. Information is provided in module 1.
7.	Does the section contain controls for drug substance?	X		
8.	Does the section contain controls for drug product?	X		
9.	Has the stability data and analysis been provided to support the proposed expiry?	X		
10.	Has all the information requested during the IND phase, and the pre-NDA meetings been included?	X		
11.	Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional labeling policies, and the design of the development package?	X		
12.	Has an investigational formulations section been provided?	X		In section 3.2.P.2.2.1.2.
13.	Has the applicant provided a method validation package?	X		Module 3, Section 3.2R
14.	Is a separate microbiological section included?			Not applicable

Drug Master Files (DMFs):

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMETNS
	IV			10/8/07	Compositions and specifications are provided in the NDA.
	III			5/2/06	*
	III			5/3/06	*
	III			5/25/07	*
	III			4/17/06	*

b(4)

\*See 74-Day letter for the CMC request for appropriate testing results. references and )

Reviewer: Sue-Ching Lin Date: 05-FEB-2008

Branch Chief: Ravi Harapanhalli, Ph.D. Date: 07-FEB-2008

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Sue Ching Lin  
2/7/2008 04:33:45 PM  
CHEMIST

Ravi Harapanhalli  
2/11/2008 06:46:04 PM  
CHEMIST

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Application : NDA 22291/000  
Org Code : 160  
Priority: 1P

Sponsor: GLAXOSMITHKLINE  
NO CITY, , XX

Stamp Date: 19-DEC-2007  
PDUFA Date : 19-JUN-2008

Brand Name : PROMACTA  
Estab. Name:  
Generic Name: ELTROMBOPAG OLAMINE  
Dosage Form: (TABLET)  
Strength: 25 MG & 50 MG

Action Goal:  
District Goal: 20-APR-2008

FDA Contacts:	A. KACUBA	Project Manager	301-796-1381
	S. LIN	Review Chemist	301-796-1403
	R. HARAPANHALLI	Team Leader	301-796-1676

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Overall Recommendation: ACCEPTABLE on 30-MAY-2008 by S. ADAMS (HFD-325) 301-796-3193

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Establishment : CFN : 9610411      FEI : 3003262904  
GLAXO OPERATIONS UK LIMITED  
PRIORITY STREET  
WARE, HERTFORDSHIRE, , UK

DMF No:                              AADA:

Responsibilities:    FINISHED DOSAGE MANUFACTURER  
                          FINISHED DOSAGE PACKAGER  
                          FINISHED DOSAGE RELEASE TESTER  
                          FINISHED DOSAGE STABILITY TESTER

Profile     :    TCM                              OAI Status:    NONE  
Last Milestone:    OC RECOMMENDATION  
Milestone Date:    10-MAR-08  
Decision    :    ACCEPTABLE  
Reason     :    DISTRICT RECOMMENDATION

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Establishment : CFN : 9610414      FEI :  
GLAXO WELLCOME OPERATIONS UK  
DA1 5AH  
DARTFORD, KENT, UK

DMF No:                              AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER  
DRUG SUBSTANCE RELEASE TESTER  
DRUG SUBSTANCE STABILITY TESTER

Profile : CSN OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 10-MAR-08  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

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Establishment : CFN : 1033964 FEI : 1033964  
GLAXOSMITHKLINE INC  
1011 NORTH ARENDELL AVE  
ZEBULON, NC 275971217

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER  
FINISHED DOSAGE PACKAGER

Profile : TCM OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 05-MAR-08  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

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Establishment : CFN : FEI : \_\_\_\_\_

| | |

b(4)

DMF No: AADA:

Responsibilities: | | \

Profile : CSN OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 10-MAR-08  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

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Establishment : CFN : \_\_\_\_\_ FEI : \_\_\_\_\_

| |

b(4)

DMF No:

AADA:

Responsibilities: \_\_\_\_\_

Profile : CSN OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 10-MAR-08  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

b(4)

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Establishment : CFN \_\_\_\_\_ FEI :

DMF No:

AADA:

Responsibilities: \_\_\_\_\_

Profile : CTX OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 30-MAY-08  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

b(4)