CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207027Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 207027 SUPPL # HFD # 161

Trade Name Promacta®

Generic Name eltrombopag

Applicant Name Novartis Pharmaceuticals

Approval Date, If Known 8/24/15

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

6 months

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☒ NO ☐

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

Yes

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 022291 Promacta Tablets

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the

answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1: PETIT: A three part, staggered cohort, open-label and double blind, randomized, placebo controlled study to investigate the efficacy, safety, tolerability and pharmacokinetics of eltrombopag, a thrombopoietin receptor agonist, in previously treated pediatric patients with chronic idiopathic thrombocytopenic purpura (ITP).

Investigation #2: PETIT2: A two-part, double-blind, randomized, placebo controlled and open-label study to investigate the efficacy, safety and tolerability of eltrombopag, a thrombopoietin receptor agonist, in pediatric patients with previously treated chronic immune(idiopathic) thrombocytopenic purpura (ITP).

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	PETIT	YES ☒	NO ☐
Investigation #2	PETIT2	YES ☒	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Investigation # 1 and Investigation #2 for NDA 022291/S-015 Promacta.

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	PETIT	YES ☐	NO ☒
Investigation #2	PETIT2	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 63293	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 63293	YES ☒	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Kimberly Scott, Reviewed by T. Carioti, A.Baird, 8/24/15
Title: Regulatory Project Manager
Date: August 24, 2015

Name of Office/Division Director signing form: CDER/OHOP/DHP/Ann T. Farrell
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

KIMBERLY L SCOTT
08/24/2015

ANN T FARRELL
08/24/2015

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 207027 Supplement Number: NDA Supplement Type (e.g. SE5):

Division Name:Hematology I PDUFA Goal Date: August 2 Stamp Date: 2/24/2015

Proprietary Name: Promacta

Established/Generic Name: eltrombopag

Dosage Form: oral suspension

Applicant/Sponsor: Novartis Pharmaceuticals Corporation

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) thrombocytopenia in adult and pediatric patients 6 years and older with chronic immune (idiopathic) t

(2) thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-b

(3) patients with severe aplastic anemia who have had an insufficient response to immunosuppressive t

(4)

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: thrombocytopenia in adult and pediatric patients 1 year and older with chronic immune (idiopathic)

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: Supplement #: PMR #:

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☒ indication(s); ☒ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☒ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed):
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	wk. mo.	wk. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed):

* Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	wk. mo.	wk. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy):						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason:

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	wk. mo.	wk. mo.	Yes ☐	No ☐
☐	Other	yr. mo.	yr. mo.	Yes ☐	No ☐
☐	Other	yr. mo.	yr. mo.	Yes ☐	No ☐
☐	Other	yr. mo.	yr. mo.	Yes ☐	No ☐
☐	Other	yr. mo.	yr. mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	wk. mo.	wk. mo.
☐	Other	yr. mo.	yr. mo.
☐	Other	yr. mo.	yr. mo.
☐	Other	yr. mo.	yr. mo.
☐	Other	yr. mo.	yr. mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	wk. mo.	wk. mo.	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2:

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed):
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	wk. mo.	wk. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed):

* Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the

PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	wk. mo.	wk. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy):						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason:

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	wk. mo.	wk. mo.	Yes ☐	No ☐
☐	Other	yr. mo.	yr. mo.	Yes ☐	No ☐
☐	Other	yr. mo.	yr. mo.	Yes ☐	No ☐
☐	Other	yr. mo.	yr. mo.	Yes ☐	No ☐
☐	Other	yr. mo.	yr. mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	wk. mo.	wk. mo.
☐	Other	yr. mo.	yr. mo.
☐	Other	yr. mo.	yr. mo.
☐	Other	yr. mo.	yr. mo.
☐	Other	yr. mo.	yr. mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	wk. mo.	wk. mo.	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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

/s/

KIMBERLY L SCOTT
08/19/2015
Pediatric Page

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 207027 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: PROMACTA Established/Proper Name: eltrombopag Dosage Form: Oral suspension		Applicant: Novartis Agent for Applicant (if applicable):
RPM: Kimberly Scott, RN		Division: CDER/OHOP/DHP

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is August 24, 2015	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): Thrombopoietin receptor antagonist
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☐ Breakthrough Therapy designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☒ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☒ MedGuide w/o REMS
☒ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other BURST and IA
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters

❖ Copies of all action letters *(including approval letter with final labeling)*	Action Letter: August 24, 2015

Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	N/A
❖ Labeling reviews *(indicate dates of reviews)*	RPM: May 8, 2015 DMEPA: ☒ August 21(2), 2015 and July 14, 2015 DMPP/PLT: August 13, 2015 OPDP: August 5, 2015 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	April 29, 2015 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Pediatrics *(approvals only)* • Date reviewed by PeRC : NA If PeRC review not necessary, explain: orphan designation	Memo to file: August 19, 2015
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	August 21(2), 20, 19, 17, 14(4), 12(2), 10, and 4, 2015 July 23, 22, 13, and 6, 2015; June 25(2), 9, and 2, 2015 May 29(2) and 20, 2015; April 24 16, and 13, 2015; March 27 26, 25, 23, and 6, 2015
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	Preliminary meeting comments dated May 19, 2014
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	EOP2/CMC meeting dated March 22, 2012
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	August 17, 2015
Cross-Discipline Team Leader Review *(indicate date for each review)*	August 6, 2015
PMR/PMC Development Templates *(indicate total number)*	2 CMC PMCs
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No, separate review co-signed review dated July 31, 2015
• Clinical review(s) *(indicate date for each review)*	July 31, 2015
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See page 17 of clinical review dated July 31, 2015
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A

❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review co-signed review dated July 15, 2015
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review co-signed review dated July 15, 2015
Statistical Review(s) *(indicate date for each review)*	July 15, 2015
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review co-signed review dated August 1, 2015
Clinical Pharmacology review(s) *(indicate date for each review)*	August 1, 2015
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	August 19, 2015
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	August 4, 2015
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	August 19, 2015
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	July 31, 2015
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	Facility Inspection: August 17, 2015 Testing and Research: July 28, 2015 CDRH: July 13, 2015 Product Quality Micro: July 1, 2015
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	August 19, 2015
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable August 20, 2015 Re-evaluation date: September 30, 2015 ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☐ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

Scott, Kimberly

From: Scott, Kimberly
Sent: Friday, August 21, 2015 4:01 PM
To: 'williams, dennis'
Subject: RE: NDA 207027 Promacta Packet Label for (b) (4) Agrees

Dennis,

Thank you for informing the Agency you will be formally submitting the revised (b) (4) label to the NDA today.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
10903 New Hampshire Avenue, Bldg 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: williams, dennis [mailto:dennis.williams@novartis.com]
Sent: Friday, August 21, 2015 3:59 PM
To: Scott, Kimberly
Cc: Miller, Mara Bauman
Subject: RE: NDA 207027 Promacta Packet Label for (b) (4): Agrees

Hi Kim,

There will be no further edits and Novartis agrees to the draft label. We will formally submit the revised (b) (4) label to the NDA later today.

Thanks,
Dennis

From: Scott, Kimberly [mailto:Kimberly.Scott@fda.hhs.gov]
Sent: Friday, August 21, 2015 3:55 PM
To: williams, dennis
Cc: Miller, Mara Bauman
Subject: NDA 207027 Promacta Packet Label for (b) (4): Agrees
Importance: High

Good afternoon Dennis,

The Agency accepts the revised draft packet label for the (b) (4) for NDA 207027 Promacta. Please send an email stating there are no further edits and that Novartis agrees to the attached label, and then formally submit to the NDA.

Please confirm receipt of this email.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
10903 New Hampshire Avenue, Bldg 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: williams, dennis [mailto:dennis.williams@novartis.com]
Sent: Friday, August 21, 2015 3:14 PM
To: Scott, Kimberly
Subject: RE: Great! Thank you!

Hi Kim,

The draft packet label is attached. It includes lot and expiration date. The text (b) (4) will not appear on the actual label; this text is for internal purposes.

Thanks,
Dennis

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

/s/

KIMBERLY L SCOTT
08/24/2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Friday, August 21, 2015 12:18 PM
To: dennis.williams@novartis.com
Cc: Miller, Mara Bauman; Scott, Kimberly
Subject: NDA 207027 Promacta (b) (4) - FDA edits: DUE 2:00pm today

Importance: High

Tracking:

Recipient	Read
dennis.williams@novartis.com	
Miller, Mara Bauman	
Scott, Kimberly	Read: 8/21/2015 12:21 PM

Good morning Dennis,

The Agency has proposed additional revisions to the package label (b) (4) for NDA 207027 Promacta:

- Please ensure lot number and expiration date appears on the (b) (4)
- Ensure to remove statement (b) (4) as this statement does not have any significance and clutters the principle display panel.
- Add the storage information to the (b) (4) label. If needed, the side and back of the packet label can be used to accommodate placement of that information.

The Agency requests Novartis accept all the changes which you agree, send back the package label (b) (4) with the changes, and then officially submit to your NDA via the gateway. If you do not agree with the requested edits, please provide your comments, and proposed language (shown in tracked changes).

The Agency is requesting your response by 2:00PM (ET), this afternoon.

Please acknowledge receipt of this email.

Regards,
Kimberly
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
10903 New Hampshire Avenue, Bldg 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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

/s/

KIMBERLY L SCOTT
08/24/2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Thursday, August 20, 2015 11:25 AM
To: dennis.williams@novartis.com
Cc: Miller, Mara Bauman; Scott, Kimberly
Subject: NDA 207027 Promacta: USPI/MG/IFU: Due 2PM
Attachments: Novartis 8 19 15 draft-clean-MG-IFU.doc.docx; Novartis 8 19 15 draft-clean-PI.DOCX; NDA 207027 FDA Edits draft-25mg-x-30-packet-inner-ctn-PfOS.pdf; NDA 207027 FDA Edits draft-25mg-outer-ctn-PfOS.pdf

Importance: High

Tracking:

Recipient	Read
dennis.williams@novartis.com	
Miller, Mara Bauman	
Scott, Kimberly	Read: 8/20/2015 11:25 AM

Good morning Dennis,

Please refer to attached NDA 207027 Promacta's USPI, Medication Guide, and Instructions for Use. The Agency accepts the proposed edits from Novartis. Attached are the agreed upon USPI, Medication Guide, and Instructions for Use, and carton contain labeling. We request you officially submit these documents to your NDA by 2:00pm today.

Please acknowledge receipt of this email

Thank you,
Kim

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

45 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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.

/s/

KIMBERLY L SCOTT
08/20/2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Friday, August 21, 2015 4:01 PM
To: 'williams, dennis'
Subject: RE: NDA 207027 Promacta Packet Label for (b) (4): Agrees

Dennis,

Thank you for informing the Agency you will be formally submitting the revised (b) (4) label to the NDA today.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
10903 New Hampshire Avenue, Bldg 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: williams, dennis [mailto:dennis.williams@novartis.com]
Sent: Friday, August 21, 2015 3:59 PM
To: Scott, Kimberly
Cc: Miller, Mara Bauman
Subject: RE: NDA 207027 Promacta Packet Label for (b) (4): Agrees

Hi Kim,

There will be no further edits and Novartis agrees to the draft label. We will formally submit the revised (b) (4) label to the NDA later today.

Thanks,
Dennis

From: Scott, Kimberly [mailto:Kimberly.Scott@fda.hhs.gov]
Sent: Friday, August 21, 2015 3:55 PM
To: williams, dennis
Cc: Miller, Mara Bauman
Subject: NDA 207027 Promacta Packet Label for (b) (4): Agrees
Importance: High

Good afternoon Dennis,

The Agency accepts the revised draft packet label for the (b) (4) for NDA 207027 Promacta. Please send an email stating there are no further edits and that Novartis agrees to the attached label, and then formally submit to the NDA.

Please confirm receipt of this email.

Scott, Kimberly

From: Scott, Kimberly
Sent: Wednesday, August 19, 2015 9:01 AM
To: dennis.williams@novartis.com
Cc: Miller, Mara Bauman; Scott, Kimberly
Subject: NDA 207027 Promacta: USPI/MG/IFU; DUE 1:00PM (ET)
Attachments: NDA 207027 FDA FINAL draft-annotated-MG-IFU.docx; NDA207027 FDA FINAL draft-annotated-PI.doc

Importance: High

Good afternoon Dennis,

Please find attached the FDA's proposed revisions to the USPI, Medication Guide, and Instructions for Use for NDA 207027 Promacta. The FDA requests Novartis accept all the changes which you agree, and send back a clean version with dates. If you do not agree with the requested edits, please provide your comments, and proposed language (shown in tracked changes). If necessary, edit the text, but do not "reject" the FDA proposed changes.

The Agency is requesting your response by 1:00PM (ET), this afternoon.

Please acknowledge receipt of this email.

Regards,
Kimberly
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
10903 New Hampshire Avenue, Bldg 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

41 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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.

/s/

KIMBERLY L SCOTT
08/19/2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Monday, August 17, 2015 4:12 PM
To: dennis.williams@novartis.com
Cc: Miller, Mara Bauman
Subject: NDA 207027 Promacta: FDA requests: DUE tomorrow, 12 noon

Good afternoon Dennis,

Thank you for sending the justification on timelines for Promacta's development time necessary to develop the 12.5 mg presentation The FDA acknowledges that the proposed timelines may be reduced if development of the 12.5 mg stickpack is quickly resolved. FDA will accept 3 months stability data to support fulfillment of PMC #1 and proposes the following PMC Schedule Milestones:

Development Plan Submission:	12/2015
Development study completion	12/2017
Final Report/Supplement Submission:	3/2018"

Please let me know me if Novartis concurs with this revised scheduled by no later than 12noon (ET) tomorrow, August 18, 2015.

Please acknowledge receipt of this email.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
10903 New Hampshire Avenue, Bldg 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Miller, Mara Bauman
Sent: Monday, August 17, 2015 2:56 PM
To: Scott, Kimberly
Subject: RE: : NDA 207027 Promacta: Novartis response to PMC development time

- Ask Novartis to send in the agreed PMC language to the NDA.
- Update the PMR/PMC templates with the agreed language and dates. Also put the agreed language and dates into the action letter
- We will create the PMC set tomorrow (I am flexi, but we can do via webex) and then you can update the letter

Thanks,
Mara

From: Scott, Kimberly
Sent: Monday, August 17, 2015 2:43 PM
To: Kwitkowski, Virginia; Ehrlich, Lori; Brown, Janice; Stephens, Olen; Kane, Robert; Lee, Jee Eun; Patel, Hasmukh B; Habtemariam, Bahru; Farrell, Ann T
Cc: Leaman, Diane V; Miller, Mara Bauman; Laiq, Rabiya
Subject: : NDA 207027 Promacta: Novartis response to PMC development time

Good afternoon Team,

Novartis has responded to our request to justify the time necessary to develop the 12.5 mg presentation for the same fill material. They have agreed to accept the term "development study completion."

Please see the email below, and let me know how you would like to proceed.

Thank you,
Kim

From: williams, dennis [mailto:dennis.williams@novartis.com]
Sent: Monday, August 17, 2015 2:25 PM
To: Scott, Kimberly
Cc: Miller, Mara Bauman
Subject: RE: NDA 207027 Promacta: FDA requests due Monday, 8/14

Hi Kim,

We will accept the term "development study completion." in the final PMC wording. Attached is the justification for the development time necessary to develop the 12.5 mg presentation.

(b) (4)

(b) (4)

Thanks,
Dennis

From: Scott, Kimberly [mailto:Kimberly.Scott@fda.hhs.gov]
Sent: Friday, August 14, 2015 5:28 PM
To: williams, dennis
Cc: Miller, Mara Bauman
Subject: NDA 207027 Promacta: FDA requests due Monday, 8/14
Importance: High

Good evening Dennis,

The Agency requests the following information for NDA 207027 Promacta's PMC's by noon, Monday, August 14, 2015:

- Accept the term "development study completion."
- Please justify the amount of development time necessary to develop a 12.5 mg presentation for the same fill material.

Please acknowledge receipt of this email.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
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From: williams, dennis [mailto:dennis.williams@novartis.com]
Sent: Friday, August 14, 2015 3:38 PM
To: Scott, Kimberly
Cc: Miller, Mara Bauman
Subject: RE: NDA 207027 Promacta: Post Marketing Commitments Milestones

Hello Kim,

We agree to the 2 requested PMCs listed below. Attached below is the milestone dates proposed by Novartis. For the purposes of the "Development Completion" we are considering this the date when development work is completed (e.g., stability batches available) and for "Study Completion" we are considering this the date when the study/experiment is completed/data available.

For additional information, the dates for PMC#1 are based on (b) (4) months of development work plus (b) (4) months to generate stability.

Thanks,

Dennis

PMC #1 Description:
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 Schedule Milestones:

Development Plan Submission:	12/2015
Development Completion:	08/2018
Final Report/Supplement Submission:	12/2018

PMC #2 Description:
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.)

PMC Schedule Milestones:

Final Protocol/Plan Submission:	12/2015
Study Completion:	04/2016
Final Report Submission:	06/2016

From: Scott, Kimberly [mailto:Kimberly.Scott@fda.hhs.gov]
Sent: Friday, August 14, 2015 12:42 PM
To: williams, dennis
Cc: Miller, Mara Bauman
Subject: NDA 207027 Promacta: Post Marketing Commitments Milestones
Importance: High

Hi Dennis,

The protocol submission would be once you submit your formal acceptance of the PMC to the NDA. The "study start" would be the time you begin your study for the requested post marketing commitment.

PMC #1 Description: 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 Schedule Milestones:
Development Plan Submission: _____
Development Completion: _____
Final Report/Supplement Submission: _____

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PMC Schedule Milestones:
Final Protocol/Plan Submission: _____
Study Completion: _____
Final Report Submission: _____

Please confirm receipt of this email, and let me know if you have any questions.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
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Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
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From: williams, dennis [mailto:dennis.williams@novartis.com]
Sent: Friday, August 14, 2015 9:22 AM
To: Scott, Kimberly
Cc: Miller, Mara Bauman
Subject: RE: NDA 207027 Promacta: Post Marketing Commitments: Respond by 8/14

Hi Kim,

We plan to send back our agreement to both PMCs later today. I have a question that will help us better confirm our proposed dates.

For both PMC#1 and #2, I am not otally clear what is the FDA expectation for "protocol submission" and "study start" since these are CMC/technical activities rather than a clinical protocol/study. Once I have a better understanding of what these milestones mean, we will be able to confirm dates.

Thanks,
Dennis

From: Scott, Kimberly [mailto:Kimberly.Scott@fda.hhs.gov]
Sent: Monday, August 10, 2015 1:51 PM
To: williams, dennis
Cc: Miller, Mara Bauman
Subject: NDA 207027 Promacta: Post Marketing Commitments: Respond by 8/14
Importance: High

Good afternoon Dennis,

As we continue our review of your Application, our normal policy is to consider post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following post-marketing commitments (PMCs) are necessary based on the data available to date. These brief descriptions are intended to describe the main objective and characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key elements and timelines. We are available to discuss by teleconference if needed. For any new studies, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol AND have already received full concurrence by the Division, that the protocol is considered acceptable to address the PMC.

Upon mutual agreement on the PMC description and timeline, we ask you to submit both by email and officially a copy of PMCs to us with a statement that you agree to perform the studies as described and within the

timelines that you specify. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Final PMC designation numbers will be assigned later. Provide a response by Friday August 14, 2015 at 12:00 PM.

PMC #1 Description:	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 Schedule Milestones:	Final Protocol Submission:	11/2015
	Study/Trial Completion:	03/2016
	Final Report Submission:	05/2016

PMC #2 Description:	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.)	
PMC Schedule Milestones:	Final Protocol Submission:	11/2015
	Study/Trial Completion:	01/2016
	Final Report Submission:	03/2016

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Thank you,
Kim
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Regulatory Health Project Manager
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Center for Drug Evaluation and Research|Food and Drug Administration
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Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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/s/

KIMBERLY L SCOTT
08/17/2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Friday, August 14, 2015 5:28 PM
To: dennis.williams@novartis.com
Cc: Miller, Mara Bauman
Subject: NDA 207027 Promacta: FDA requests due Monday, 8/14

Importance: High

Good evening Dennis,

The Agency requests the following information for NDA 207027 Promacta's PMC's by noon, Monday, August 14, 2015:

- Accept the term "development study completion."
- Please justify the amount of development time necessary to develop a 12.5 mg presentation for the same fill material.

Please acknowledge receipt of this email.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
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Sent: Friday, August 14, 2015 3:38 PM
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Cc: Miller, Mara Bauman
Subject: RE: NDA 207027 Promacta: Post Marketing Commitments Milestones

Hello Kim,

We agree to the 2 requested PMCs listed below. Attached below is the milestone dates proposed by Novartis. For the purposes of the "Development Completion" we are considering this the date when development work is completed (e.g., stability batches available) and for "Study Completion" we are considering this the date when the study/experiment is completed/data available.

For additional information, the dates for PMC#1 are based on (b) (4) months of development work plus (b) (4) months to generate stability.

Thanks,

Dennis

PMC #1 Description:
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PMC Schedule Milestones:

Development Plan Submission:	12/2015
Development Completion:	08/2018
Final Report/Supplement Submission:	12/2018

PMC #2 Description:
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.)

PMC Schedule Milestones:

Final Protocol/Plan Submission:	12/2015
Study Completion:	04/2016
Final Report Submission:	06/2016

From: Scott, Kimberly [mailto:Kimberly.Scott@fda.hhs.gov]
Sent: Friday, August 14, 2015 12:42 PM
To: williams, dennis
Cc: Miller, Mara Bauman
Subject: NDA 207027 Promacta: Post Marketing Commitments Milestones
Importance: High

Hi Dennis,

The protocol submission would be once you submit your formal acceptance of the PMC to the NDA. The "study start" would be the time you begin your study for the requested post marketing commitment.

PMC #1 Description: 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 Schedule Milestones:
Development Plan Submission: _____
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Final Report/Supplement Submission: _____

PMC #2 Description: 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.)

PMC Schedule Milestones:
Final Protocol/Plan Submission: _____
Study Completion: _____
Final Report Submission: _____

Please confirm receipt of this email, and let me know if you have any questions.

Thank you,
Kim
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Division of Hematology Products|Office of Hematology and Oncology Products
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From: williams, dennis [mailto:dennis.williams@novartis.com]
Sent: Friday, August 14, 2015 9:22 AM
To: Scott, Kimberly
Cc: Miller, Mara Bauman
Subject: RE: NDA 207027 Promacta: Post Marketing Commitments: Respond by 8/14

Hi Kim,

We plan to send back our agreement to both PMCs later today. I have a question that will help us better confirm our proposed dates.

For both PMC#1 and #2, I am not otally clear what is the FDA expectation for "protocol submission" and "study start" since these are CMC/technical activities rather than a clinical protocol/study. Once I have a better understanding of what these milestones mean, we will be able to confirm dates.

Thanks,
Dennis

From: Scott, Kimberly [mailto:Kimberly.Scott@fda.hhs.gov]
Sent: Monday, August 10, 2015 1:51 PM
To: williams, dennis
Cc: Miller, Mara Bauman
Subject: NDA 207027 Promacta: Post Marketing Commitments: Respond by 8/14
Importance: High

Good afternoon Dennis,

As we continue our review of your Application, our normal policy is to consider post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following post-marketing commitments (PMCs) are necessary based on the data available to date. These brief descriptions are intended to describe the main objective and characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key elements and timelines. We are available to discuss by teleconference if needed. For any new studies, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol AND have already received full concurrence by the Division, that the protocol is considered acceptable to address the PMC.

Upon mutual agreement on the PMC description and timeline, we ask you to submit both by email and officially a copy of PMCs to us with a statement that you agree to perform the studies as described and within the

timelines that you specify. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Final PMC designation numbers will be assigned later. Provide a response by Friday August 14, 2015 at 12:00 PM.

PMC #1 Description:	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 Schedule Milestones:	Final Protocol Submission:	11/2015
	Study/Trial Completion:	03/2016
	Final Report Submission:	05/2016

PMC #2 Description:	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.)	
PMC Schedule Milestones:	Final Protocol Submission:	11/2015
	Study/Trial Completion:	01/2016
	Final Report Submission:	03/2016

Please acknowledge receipt of this email, and let me know if you have any questions.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
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Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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/s/

KIMBERLY L SCOTT
08/14/2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Friday, August 14, 2015 5:35 PM
To: 'dennis.williams@novartis.com'
Cc: Miller, Mara Bauman
Subject: NDA 207027 Promacta: USPI/MG/IFU: review DUE COB Monday, 8/17
Attachments: NDA 207027 FDA USPI Edits for Novartis 8 14 15.doc; NDA 207027 Promacta MG IFU FDA edits Aug 14 15 marked.docx

Good afternoon Dennis,

Please refer to Promacta, NDA 207027 submitted February 24, 2015, and reference made to the updated USPI label to the Agency on August 10, 2015. Please find attached the FDA's proposed revision to Novartis' submission for a new formulation of Promacta (for oral suspension, and provides for a new indication "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."

The FDA has proposed edits with comments embedded within the document. Please review and provide revisions or comments to the attached FDA USPI, Medication Guide, and Instructions For Use. Using the same document, please remember to "save" your changes, and provide your comments in the following manner:

- ***Medication Guide and Instructions for Use***:
  - It is important that you not change the formatting of the MG/IFU as this is the formatting by the Agency.
  - Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing.

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, and proposed language (shown in tracked changes). If necessary, edit the text but do not "reject" the FDA-proposed changes.

We request your response by 5:00PM (ET), **Monday, August 17, 2015.** Please acknowledge receipt of this email.

Regards,
Kimberly
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
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/s/

KIMBERLY L SCOTT
08/14/2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Friday, August 14, 2015 1:21 PM
To: dennis.williams@novartis.com
Cc: Scott, Kimberly; Miller, Mara Bauman
Subject: NDA 207027 and NDA 022291 Promacta: Pediatric Exclusivity Granted

Importance: High

Good morning Dennis,

Pediatric Exclusivity has been granted for studies conducted on Promacta (eltrombopag), effective August 14, 2015, under section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a). This information will be reflected on CDER's pediatric web site and in the monthly update of the Orange Book.

In accordance with section 505A(e)(1) of the Act, as amended by the FDA Amendments Act (Pub. L. No. 110-85), approved drugs for which a pediatric exclusivity determination was made on or after September 27, 2007, shall have a copy of the Written Request and any amendments posted on CDER's pediatric web site.

In addition, we remind you that section 17 of the BPCA, as reauthorized and amended under the FDA Safety & Innovation Act (Pub. L. No. 112-144), requires for 18 months after pediatric labeling is approved, any report received by FDA of an adverse event associated with the drug granted exclusivity will be referred to the Office of Pediatric Therapeutics. This process occurs for all products granted Pediatric Exclusivity regardless of the regulatory action taken. The Director of that Office will provide for a review of the adverse event reports by the Pediatric Advisory Committee (PAC) and will obtain recommendations from that Committee on the action FDA should take.

Please acknowledge receipt of this email.

Thank you,
Kimberly
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Product
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
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/s/

KIMBERLY L SCOTT
08/14/2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Friday, August 14, 2015 12:42 PM
To: 'williams, dennis'
Cc: Miller, Mara Bauman
Subject: NDA 207027 Promacta: Post Marketing Commitments Milestones

Importance: High

Hi Dennis,

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PMC #1 Description: 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 Schedule Milestones:
Development Plan Submission: _____
Development Completion: _____
Final Report/Supplement Submission: _____

PMC #2 Description: 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.)

PMC Schedule Milestones:
Final Protocol/Plan Submission: _____
Study Completion: _____
Final Report Submission: _____

Please confirm receipt of this email, and let me know if you have any questions.

Thank you,
Kim
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Sent: Friday, August 14, 2015 9:22 AM
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Cc: Miller, Mara Bauman
Subject: RE: NDA 207027 Promacta: Post Marketing Commitments: Respond by 8/14

Hi Kim,

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Dennis

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Sent: Monday, August 10, 2015 1:51 PM
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Cc: Miller, Mara Bauman
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Importance: High

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Thank you,
Kim

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Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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/s/

KIMBERLY L SCOTT
08/14/2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Wednesday, August 12, 2015 11:15 AM
To: dennis.williams@novartis.com
Cc: Miller, Mara Bauman; Scott, Kimberly
Subject: NDA 207027 Promacta: Agency Response to PMC question

Importance: High

Good morning Dennis,

The review division believes that a 12.5 mg strength is needed in the event that dose reduction or incremental dose adjustments of 12.5mg are required. We suspect that caregivers, to avoid wasting drug (and saving money) may be tempted to save the remaining portion of a 25 mg stickpack after reconstitution if the child only requires a 12.5 mg dose or some interim increment that requires a 12.5 mg dose portion. As you know, saving the reconstituted drug and administering it beyond 30 minutes is not safe because of the formation of genotoxic impurities. To avoid the potential for storing the reconstituted drug product and ingestion of a product with genotoxic impurities, a lower strength is needed. The development of a 12.5 mg strength would avoid the need to waste half of the prepared product.

Please acknowledge receipt of this email.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
10903 New Hampshire Avenue, Bldg 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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/s/

KIMBERLY L SCOTT
08/12/2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Wednesday, August 12, 2015 11:02 AM
To: dennis.williams@novartis.com
Cc: Miller, Mara Bauman; Scott, Kimberly
Subject: NDA 207027 Promacta FDA Edits to Carton Container Label: DUE Friday, 8/14
Attachments: NDA 207027 FDA Edits draft-25mg-outer-ctn-PfOS.pdf; NDA 207027 FDA Edits draft-25mg-x-30-packet-inner-ctn-PfOS.pdf

Good morning Dennis,

Regarding the carton labeling, there is an extra zero (32.0) versus 32 mg of eltrombopag in the content sentence of the carton labeling. Please update the 32.0 to 32 mg and submit the revised carton labeling to the NDA by noon, Friday 8/14/2015.

Please acknowledge receipt of this email.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
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/s/

KIMBERLY L SCOTT
08/12/2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Monday, August 10, 2015 1:51 PM
To: dennis.williams@novartis.com
Cc: Miller, Mara Bauman
Subject: NDA 207027 Promacta: Post Marketing Commitments: Respond by 8/14

Importance: High

Good afternoon Dennis,

As we continue our review of your Application, our normal policy is to consider post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following post-marketing commitments (PMCs) are necessary based on the data available to date. These brief descriptions are intended to describe the main objective and characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key elements and timelines. We are available to discuss by teleconference if needed. For any new studies, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol AND have already received full concurrence by the Division, that the protocol is considered acceptable to address the PMC.

Upon mutual agreement on the PMC description and timeline, we ask you to submit both by email and officially a copy of PMCs to us with a statement that you agree to perform the studies as described and within the timelines that you specify. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Final PMC designation numbers will be assigned later. Provide a response by Friday August 14, 2015 at 12:00 PM.

PMC #1 Description: 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 Schedule Milestones:		
	Final Protocol Submission:	11/2015
	Study/Trial Completion:	03/2016
	Final Report Submission:	05/2016

PMC #2 Description: 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.)

PMC Schedule Milestones:		
	Final Protocol Submission:	11/2015
	Study/Trial Completion:	01/2016
	Final Report Submission:	03/2016

Please acknowledge receipt of this email, and let me know if you have any questions.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
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/s/

KIMBERLY L SCOTT
08/10/2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, August 04, 2015 2:38 PM
To: dennis.williams@novartis.com
Cc: Miller, Mara Bauman; Scott, Kimberly
Subject: NDA 207027 Promacta Edits to USPI- DUE August 11, 2015
Attachments: NDA_207027 Promacta FDA Edits_8_4_2015.doc

Importance: High

Good afternoon Dennis,

Please refer to Promacta, NDA 207027 submitted February 24, 2015, and reference made to the updated USPI label to the Agency on July 24, 2015. Please find attached the FDA's proposed revision to Novartis' submission for a new formulation of Promacta (for oral suspension, and provides for a new indication "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."

The FDA has proposed edits with comments embedded within the document. Please review and provide revisions or comments to the attached FDA USPI. Using the same document, please remember to "save" your changes, and provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, and proposed language (shown in tracked changes). If necessary, edit the text but do not "reject" the FDA-proposed changes.

We request your response by 2:00PM (ET), **Tuesday, August 11, 2015.** Please note: The Medication Guide and Instructions for Use are under review by other offices and further comments on those sections will be sent at a later date.

Please acknowledge receipt of this email.

Regards,
Kimberly
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
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49 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

KIMBERLY L SCOTT
08/04/2015

From: Miller, Mara Bauman
To: "williams, dennis"; Scott, Kimberly
Cc: Tzeng, Linhua
Subject: RE: NDA 207027 Promacta: Agency requests Due 7/24
Date: Thursday, July 23, 2015 11:04:00 AM

Hi Dennis,
Regarding your question below, we have the following response:

The Division is aware of the degradation product formation and continues to recommend against saving mixed product for future doses. Our comment was intended to mean that few patients will need less than 25 mg doses, so the chances of patients trying to save residual doses will be low.

Thank you,
Mara

From: williams, dennis [mailto:dennis.williams@novartis.com]
Sent: Thursday, July 23, 2015 10:43 AM
To: Scott, Kimberly
Cc: Tzeng, Linhua; Miller, Mara Bauman
Subject: RE: NDA 207027 Promacta: Agency requests Due 7/24

Hi Kim,

We are meeting internally today to discuss the Division's proposal for the 12.5 mg dose. One last question that may help us. In the request, it states "We have discussed this internally and are of the opinion that dose-reductions will occur much less frequently than dose-increases, and thus will provide for limited risk of "saving residual doses".

Can you confirm the issue of the degradation product formation in the reconstituted product was among the discussion points when the Division discussed the issue of the 12.5 mg dose and the risk of saving residual doses.

Thanks,
Dennis

From: Scott, Kimberly [mailto:Kimberly.Scott@fda.hhs.gov]
Sent: Wednesday, July 22, 2015 12:41 PM
To: williams, dennis
Cc: Tzeng, Linhua; Miller, Mara Bauman
Subject: FW: NDA 207027 Promacta: Agency requests Due 7/24

Hi Dennis,

Thank you for your prompt response.

Thanks,

Kim

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
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Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: williams, dennis [mailto:dennis.williams@novartis.com]
Sent: Wednesday, July 22, 2015 12:27 PM
To: Scott, Kimberly
Cc: Tzeng, Linhua
Subject: RE: NDA 207027 Promacta: Agency requests Due 7/24

Hi Kim,

Thanks. This is helpful. I can say we are fine with the proposed starting dose (request 1a) and eliminating the IFU (request 2), but I suspect the use of half the PfOS to achieve a 12.5 mg dose will require some discussion internally here.

Thanks,
Dennis

From: Scott, Kimberly [mailto:Kimberly.Scott@fda.hhs.gov]
Sent: Wednesday, July 22, 2015 12:18 PM
To: williams, dennis
Cc: Tzeng, Linhua
Subject: RE: NDA 207027 Promacta: Agency requests Due 7/24

Hi Dennis,

To clarify, we do not recommend [redacted] (b) (4) when dose reductions are needed; instead, doses of less than one 25 mg stickpack [redacted] (b) (4) Therefore, 12.5 mg daily dose would be the step down from 25 mg daily dose.

Please confirm receipt of this email.

Thank you,
Kim

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
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Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: williams, dennis [mailto:dennis.williams@novartis.com]
Sent: Wednesday, July 22, 2015 10:31 AM
To: Scott, Kimberly
Cc: Tzeng, Linhua
Subject: RE: NDA 207027 Promacta: Agency requests Due 7/24

Hi Kim,

I can confirm receipt of the request.

I'm not sure I completely understand the request 1b listed below. Is the Division requesting:

1) 12.5 mg dose reduction for any dose reduction or only for those who are currently taking 25 mg daily?
2) To achieve a 12.5 mg dose, the Division is recommending using half of a 25 mg (b) (4) mixed in 20 ml of water (i.e. 12.5 mg/10 ml)? this question is important for several reasons including noteworthy revisions to the IFU. - Yes

Thanks,
Dennis

From: Scott, Kimberly [mailto:Kimberly.Scott@fda.hhs.gov]
Sent: Wednesday, July 22, 2015 10:15 AM
To: williams, dennis
Cc: Scott, Kimberly; Tzeng, Linhua
Subject: NDA 207027 Promacta: Agency requests Due 7/24
Importance: High

Good morning Dennis,

The Agency is requesting information regarding NDA 207027 Promacta. We have the following requests:

1. Please resubmit package insert to include the following dose recommendations:
    a. Pediatric Patients Aged 1-5 (both EA and non-EA) 25 mg daily (starting dose)
    b. Dose-reductions would be 12.5mg daily (We have discussed this internally and are of the opinion that dose-reductions will occur much less frequently than dose-increases, and thus will provide for limited risk of "saving residual doses."

2. Revise IFU to eliminate (b) (4)

The Agency requests you respond by 5:00pm (ET), Friday, July 24, 2015. Please be sure to send your response to Linhua Tzeng (cc'd), and include me on all correspondences as I will be

out of the office.

Please be sure to acknowledge receipt of this email.

Thank you,
Kim

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
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/s/

MARA B MILLER
07/23/2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Wednesday, July 22, 2015 10:15 AM
To: dennis.williams@novartis.com
Cc: Scott, Kimberly; Tzeng, Linhua
Subject: NDA 207027 Promacta: Agency requests Due 7/24

Importance: High

Good morning Dennis,

The Agency is requesting information regarding NDA 207027 Promacta. We have the following requests:

1. Please resubmit package insert to include the following dose recommendations:
    a. Pediatric Patients Aged 1-5 (both EA and non-EA) 25 mg daily (starting dose)
    b. Dose-reductions would be 12.5mg daily (We have discussed this internally and are of the opinion that dose-reductions will occur much less frequently than dose-increases, and thus will provide for limited risk of "saving residual doses."

2. Revise IFU to eliminate (b) (4)

The Agency requests you respond by 5:00pm (ET), Friday, July 24, 2015. Please be sure to send your response to Linhua Tzeng (cc'd), and include me on all correspondences as I will be out of the office.

Please be sure to acknowledge receipt of this email.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
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Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

Laiq, Rabiya

From: Laiq, Rabiya
Sent: Monday, July 13, 2015 5:57 PM
To: 'williams, dennis'
Cc: Scott, Kimberly
Subject: NDA 207027 Information Request - Please Respond by July 15, 2015 COB

Dear Dr. Williams:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Promacta (eltrombopag).

We also refer to your February 24, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. On May 29, 2015 you were asked to provide test results per USP <661> for the product ancillary components for NDA 207027. You stated in your response that the dosing syringe and bottle closure test results are located in the (b) (4) DMF. You provided the DMF number and the page number (DMF# (b) (4) page 81 and DMF# (b) (4) page 45) as well as the letters of authorization for those DMF files. Please provide the volume number for the DMF files for the dosing syringe and bottle closure so that the evaluation of leachables can be done.

If you have any questions, please contact me, Rabiya Laiq, Pharm.D., Regulatory Business Process Manager, at (240) 402-6153. Please respond by July 15, 2015 or sooner.

Kindly confirm receipt.

Rabiya

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-6153
Email: rabiya.laiq@fda.hhs.gov

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/s/

KIMBERLY L SCOTT
07/22/2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Monday, July 06, 2015 11:26 AM
To: dennis.williams@novartis.com
Cc: Miller, Mara Bauman; Scott, Kimberly
Subject: NDA 207027 Promacta: Agency, Comments

Importance: High

Good morning Dennis,

Based on the teleconference held between the Agency and Novartis on June 30, 2015 regarding NDA 207027, the reviewers have comments. If Novartis chooses to have the caregivers and patients administer the dose of 12.5 mg daily (b) (4) we recommend you conduct a follow up Human Factors study that will specifically assess the ability of patients and caregivers to be able to extract correct 10 mL dose of the suspended Promacta (12.5 mg) and assess the comprehension of patients and caregivers that the product should not be re-used due to the risk associated with the re-use of the product (i.e., the re-use of the product could be assessed through a IFU comprehension task). All labeling materials (e.g., IFU) used in the Human Factors study should be in to-be-marketed finalized form.

Please acknowledge receipt of this email.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
10903 New Hampshire Avenue, Bldg 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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KIMBERLY L SCOTT
07/06/2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Thursday, June 25, 2015 8:10 AM
To: dennis.williams@novartis.com
Cc: Miller, Mara Bauman; Scott, Kimberly
Subject: NDA 207027 Promacta- TCON request Monday, June 29

Importance: High

Good morning Dennis,

The Agency is requesting a teleconference with Novartis for NDA 207027, Promacta this Monday, June 29, 2015 from 2:00pm-2:30pm. The purpose of this tcon is to discuss the findings from you Information Request response on 6/16/15 as Novartis relates to the proposed pediatric doses and formulations. If available for our requested time, please provide a teleconference number for the Agency.

Please acknowledge receipt of this email.

Thank you,
Kimberly
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
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/s/

KIMBERLY L SCOTT

06/25/2015

Request to have tcon with Sponsor regarding IR from clinical/clini pharm regarding pediatric dose and formulation from june 2

Laiq, Rabiya

From:	Laiq, Rabiya
Sent:	Thursday, June 25, 2015 4:42 PM
To:	'williams, dennis'
Cc:	Scott, Kimberly
Subject:	FDA Information Request NDA 207027- Please Respond by June 30, 2015.

Dear Dr. Williams:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Promacta (eltrombopag).

We also refer to your February 24, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. ***We still have concerns regarding the specificity of the IR method used for the identification testing of the drug substance in the drug product. The band*** (b) (4) ***in the spectrum of the drug product. Please include an additional Identification test using an orthogonal method, i.e. HPLC/UV, in the specification of the drug product.***

If you have any questions, please contact me, Rabiya Laiq, Pharm.D., Regulatory Business Process Manager, at (240) 402-6153. Please respond by June 30, 2015.

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-6153
Email: rabiya.laiq@fda.hhs.gov

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207027

INFORMATION REQUEST

Novartis Pharmaceuticals Corporation
Attention: Jiten Rana, Pharm.D.
Associate Director of Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Rana:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Promacta (eltrombopag).

We also refer to your February 24, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. We understand that your commercial batch scales may be varied to meet the production demands provided appropriate validation data are available. Please clarify what you anticipate will be the commercial batch scale range. Please also clarify if different (b) (4) will be used to accommodate the change in commercial batch size. If so, please commit to use (b) (4) testing in (b) (4) batches at the new scale to confirm that the change has no impact on these drug product critical quality attributes which are at high risk of failure due (b) (4) (b) (4)

2. According to the data submitted, the Uniformity of Dosage Unit data variability observed for batches R689806, R689808 and R689817 are higher than batches R676125 and R682935. Please clarify what, if anything, is different between these batches (raw material lots, equipment model or operating parameters, (b) (4) etc.) and explain the potential cause(s) for these observations.

If you have any questions, please contact me, Rabiya Laiq, Pharm.D., Regulatory Business Process Manager, at (240) 402-6153. Please respond by June 12, 2015.

Sincerely,

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: 2015.06.09 11:21:21 -04'00'

Janice Brown, M.S.
Quality Assessment Lead, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, June 02, 2015 8:41 AM
To: dennis.williams@novartis.com; Rana, Jiten (jiten.rana@novartis.com)
Cc: Scott, Kimberly
Subject: NDA 207027 Promacta: Information Request Due June 8

Importance: High

Good morning Dennis,

The Agency is requesting information for NDA 207027 Promacta. Please respond to the following requests:

1. Observed bioavailability of the powder formulation for oral suspension(PfOS) in healthy adults could be utilized in your population PK modeling as a fixed value, instead of estimating it. Perform modeling with this approach and compare estimated PKPD parameters with those from your final models. If you have already attempted but concluded not to pursue this approach or had rationale not to pursue, please explain.
2. Perform simulations with 12.5 mg daily dose in pediatric patients 1 to 5 years old with East Asian ancestry and compare the predicted profiles of eltrombopag concentration and platelet counts following daily dosing of the studied start dose (0.8 mg/kg) and the proposed start dose (b) (4) in these patients. Also compare the predicted profiles of eltrombopag concentration and platelet counts following daily dosing of the studied start dose (1.5 mg/kg) and the proposed start dose (25 mg) in pediatric patients 1 to 5 years old with non-East Asian ancestry. Finally compare the predicted PK and PD between patients with East Asian ancestry following 12.5 mg daily dose and those with non-East Asian ancestry following 25 mg daily dose. When the simulations are performed, include 95% prediction intervals. Submit the simulation results in figures as well as tables where predicted values are summarized. Datasets and codes used for the simulations should be submitted together.
3. Please indicate if there are any food types that are not expected to alter the absorption of PfOS formulation when eltrombopag is given concurrently with food in pediatric patients 1 to 5 years old. Submit any relevant pre-clinical or clinical food effect evaluations.

Please respond to these information requests by Monday, June 8, 2015.

Please acknowledge receipt of this email.

Thank you,
Kimberly

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
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/s/

KIMBERLY L SCOTT
06/02/2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Friday, May 29, 2015 8:32 AM
To: dennis.williams@novartis.com
Cc: Miller, Mara Bauman; Cox, Toni-Ann; Rana, Jiten (jiten.rana@novartis.com); Scott, Kimberly
Subject: NDA 207027 Promacta Information Request-Due June 1

Importance: High

Good evening Dennis,

The reviewers are requesting information regarding NDA 207027 Promacta. Here is the following information request:

- In NDA207027 3.2.P.2.4 Pharmaceutical Development, you state that an evaluation of potential leachables from the product contact ancillary components was conducted and a risk assessment was carried out to highlight areas for extractable profiling. On May 21, 2015, you provided a risk assessment in the form of a FMEA. You further state that the bottle has been tested and shown to comply with the requirements of USP<661>. Please provide the test results used to evaluate for the ancillary components per USP<661>. A leachables evaluation is critical to evaluate the safety of this device when used with children.

The Agency requests you respond by 9:00an (ET), Monday, June 1, 2015.

Please be sure to acknowledge receipt of this email.

Thank you,
Kimberly
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
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/s/

KIMBERLY L SCOTT
05/29/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207027

INFORMATION REQUEST

Novartis Pharmaceuticals Corporation
Attention: Jiten Rana, Pharm.D.
Associate Director of Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Rana:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Promacta (eltrombopag).

We also refer to your February 24, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. **Regarding specificity of the method "Identification of Eltrombopag by IR," explain the differences in second derivative between the IR spectrum of PfOS and Eltrombopag Olamine reference standard in the region** (b) (4)

2. **Provide the following information with regard to the method "Drug-related Impurities Content by HPLC"** (b) (4)

   a. **In addition to Limit of Quantitation determined at the concentration of** (b) (4) **% (reporting level), provide a determination of the Limit of Detection for eltrombopag drug-related impurities. Justify further that the impurity method is sensitive enough to accurately quantitate all potential impurities of eltrombopag.**

   b. **To fully demonstrate the specificity of the method "Drug-related Impurities Content by HPLC"** (b) (4) **, provide results of stress studies at** (b) (4) (b) (4) **conditions. Submit the chromatograms (full and expanded scale), quantitative results, and peak purity data.**

c. Justify the exclusion of any (b) (4) impurities from the Total Impurities calculation for the drug product.

If you have any questions, please contact me, Rabiya Laiq, Pharm.D., Regulatory Business Process Manager, at (240) 402-6153. Please respond by June 5, 2015.

Sincerely,

{See appended electronic signature page}

Janice Brown, M.S.
Quality Assessment Lead, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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: 2015.05.29 12:58:41 -04'00'

Scott, Kimberly

From: Scott, Kimberly
Sent: Wednesday, May 20, 2015 12:03 PM
To: dennis.williams@novartis.com
Cc: Miller, Mara Bauman; Scott, Kimberly
Subject: NDA 207027 Promacta- Information Request-Due Thursday, May 21st

Importance: High

Good afternoon Dennis,

The reviewers are requesting information regarding NDA 207027 Promacta's final Human Factor Study report I received via email on Friday, May 15, 2015. Here is the following information request:

1. Section: 3.2.P.2.4 Pharmaceutical Development, you state that an evaluation of potential leachables from the product contact ancillary components was conducted and a risk assessment was carried out to highlight areas for extractable profiling. You further state that the risk assessment found the product contact materials to be very low risk for leachable. The data for this evaluation could not be located. Please provide the leachable evaluation and risk assessment conducted for the ancillary components. A leachables evaluation is critical to evaluate the safety of this device when used with children.

2. Labeling instructions cleaning instruction state "Rinse the mixing bottle, lid, syringe, and plunger under running water and air dry." Reviewers could not locate any performance testing done to evaluate (b) (4) . Please provide results of testing demonstrating performance after 30 uses per the directions for use. Assuring that the ancillary components perform as intended is critical for accurate dosing of this medication.

The Agency requests you respond by tomorrow, 12:00noon (ET), Thursday, May 21, 2015.

Please be sure to acknowledge receipt of this email.

Thank you,
Kimberly
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
10903 New Hampshire Avenue, Bldg 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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/s/

KIMBERLY L SCOTT
05/20/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207027

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Novartis Pharmaceuticals Corporation
Attention: Shanthi Ganeshan, PhD
VP & US Head, Drug Regulatory Affairs
Oncology Business Unit
One Health Plaza
East Hanover, NJ

Dear Dr. Ganeshan:

Please refer to your New Drug Application (NDA) dated February 24, 2015, received February 24, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Promacta® (eltrombopag) (b) (4) for Oral Suspension, 25mg.

We also refer to your amendments dated April 1, 15, and 20, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is August 24, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by August 3, 2015.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide/Instructions for Use. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide/Instructions for Use, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Kimberly Scott, Regulatory Project Manager, at (240) 402-4560.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

THERESA A CARIOTI
04/24/2015
Signing on behalf of Dr. Ann Farrell

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207027

TRANSFER OF NDA OWNERSHIP

Novartis Pharmaceuticals Corporation
Attention: Shanthi Ganeshan, PhD
VP & US Head, Drug Regulatory Affairs
Oncology Business Unit
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Ganeshan:

We acknowledge the March 23, 2015, receipt of your March 23, 2015, correspondence notifying the Food and Drug Administration of the change of ownership of the following new drug application (NDA):

Name of Drug Product:	Promacta (eltrombopag) (b) (4) for Oral Suspension, 25mg
NDA Number:	207027
Name of New Applicant:	NOVARTIS PHARMACEUTICALS CORPORATION
Name of Previous Applicant:	GLAXOSMITHKLINE

Your correspondence provided the information necessary to effect this change, and we have revised our records to indicate NOVARTIS as the applicant of record for this application.

DRUG MASTER FILE LOA

If your NDA references any Drug Master Files (DMF), we request that you notify your suppliers and contractors who have DMFs referenced by your NDA of the change so that they can submit a new letter of authorization (LOA) to their Drug Master File(s) and send you a copy of the new LOAs. Please submit these copies of the LOAs to this NDA.

REPORTING REQUIREMENTS

All changes to the information in the NDA from that described by the original owner, such as manufacturing facilities and controls, must be reported to us prior to implementation. However, changes in the name of the manufacturer, packer, or distributor in the drug product's label or labeling may be reported in the next annual report. Refer to the *Guidance for Industry: Changes to an Approved NDA or ANDA* for information on reporting requirements.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 21 CFR 314.81. In addition, you are responsible for any correspondence outstanding as of the effective date of the transfer.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please call me at (240) 402-4560.

Sincerely,

{See appended electronic signature page}

Kimberly Scott, RN, BSN, OCN®
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

cc: GLAXOSMITHKLINE
DIRECTOR, GLOBAL REGULATORY AFFAIRS, ONCOLOGY
ATTN: DENNIS R. WILLIAMS, PHARMD
1250 SOUTH COLLEGEVILLE ROAD
COLLEGEVILLE, PA 19426

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/s/

KIMBERLY L SCOTT
04/16/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207027

INFORMATION REQUEST

Novartis Pharmaceuticals Corporation
Attention: Jiten Rana, Pharm.D.
Associate Director of Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Rana:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Promacta (eltrombopag).

We also refer to your February 24, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Include a test for polymorphic form of eltrombopag olamine in your drug substance specification.

2. Demonstrate the in-use physical stability of the reconstituted suspension [redacted (b) (4)]

3. Provide data that demonstrates the reconstituted suspension remains in suspension [redacted (b) (4)].

4. You claim that Xanthan gum is added to the formulation [redacted (b) (4)] Since the proposed formulation contains [redacted (b) (4)] of Xanthan gum, please provide more data, [redacted (b) (4)] data generated with the [redacted (b) (4)] samples from batches R676125, R682935, R689806, R689808 and R689817 or other commercial scale batches, to show that Xanthan gum [redacted (b) (4)] Alternatively, demonstrate that [redacted (b) (4)]

(b) (4)

(b) (4)

5. Please address the following regarding in-process stickpack (b) (4)

(b) (4)

6. Justify why a (b) (4) is necessary with supporting data.

7. In 3.2.P.3.4, you have set the in-process target stickpack fill weight (b) (4)

However, the process description/production batch record should clearly outline the calculation being used.

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

9. Provide a justification for not including a microbial enumeration test (MET) specification to include the absence of *Escherichia coli* (*E. 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>.

If you have any questions, please contact me, Rabiya Laiq, Pharm.D., Regulatory Business Process Manager, at (240) 402-6153. Please respond by May 10, 2015.

Sincerely,

{See appended electronic signature page}

Janice Brown, M.S.
Quality Assessment Lead, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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/s/

RABIYA LAIQ
04/10/2015

JANICE T BROWN
04/13/2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Friday, March 27, 2015 1:44 PM
To: dennis.q.williams@gsk.com
Cc: Miller, Mara Bauman
Subject: NDA 207027 Promacta: Due April 20

Dear Dennis,

Regarding NDA 207027 for Promacta, received February 24, 2015, we have the following request for information. Please submit a response by April 20, 2015.

Your NDA included descriptions and summary information for the device constituent parts of the combination product (reusable mixing bottle, cap and syringe). We are unable to locate specific information supporting the safety and performance of the device constituent parts of the combination product in the context of their intended use under the subject NDA. Please submit the following:

1. Information that verifies the device constituent parts of the product can perform as intended. The following list includes specific system attributes for which no associated verification information was found within the submission. Please note that this list may not include all relevant elements of device constituent part performance.
   a. Physical retention of device components and resistance to separation during use.
   b. Accuracy of the syringe and any graduated markings to deliver the required medication dose.
   c. Allowance for transfer, mixing and delivery of the medication dose.
   d. Force required attaching and detaching system components (cap/lid from bottle)
   e. Freedom from system leakage.

2. Suitability of materials used to manufacture the device constituent parts of the system. Provide information which supports that all materials present within the final finished device components are biocompatible and free from unacceptable toxicological risk in the context of their intended use.

3. Information which demonstrates that the device constituent parts are capable of meeting their intended use after a time period equal to or greater than the packaged drug product expiration date.

4. Information which demonstrates that the device constituent parts of the product are capable of meeting their intended use after being subjected to shipping and handling conditions.

5. Based on your description of the ancillary components, it appears that you are providing these devices as non- sterile. Please provide a description of the level of cleanliness associated with production and packaging of the final finished device product as well as mitigations present to ensure that the final finished product is not supplied in an unsafe or undesirable manner due to contamination.

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
10903 New Hampshire Avenue, Bldg 22, Rm 2222

Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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/s/

KIMBERLY L SCOTT
03/27/2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Thursday, March 26, 2015 9:32 AM
To: 'Dennis Williams'; Ganeshan, Shanthi (shanthi.ganeshan@novartis.com)
Cc: Miller, Mara Bauman
Subject: RE: NDA 207027 Promacta: Not met Electronic Submission Requirements for cross referencing previous submitted information

Importance: High

Good morning Dennis,

Yes, module 3.2.S includes cross reference to the NDA (example: to drug substance info previously submitted in NDA 022291). Specific sections (e.g. 3.2.S) do not include the link to the information that is cross-referenced. As discussed, please send the revisions to the module to me by email as well as through the gateway as the reviewers need this information.

Please acknowledge receipt of this email.

Thank you,
Kimberly
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
10903 New Hampshire Avenue, Bldg 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Dennis Williams [mailto:dennis.q.williams@gsk.com]
Sent: Wednesday, March 25, 2015 4:49 PM
To: Scott, Kimberly; Ganeshan, Shanthi
Cc: Miller, Mara Bauman
Subject: RE: NDA 207027 Promacta: Not met Electronic Submission Requirements for cross referencing previous submitted information

Hi Kimberly,

I can confirm receipt. Quick question; did this request originate from module 3/CMC components (e.g., x-ref back to drug substance info previously submitted in NDA 022291)?

Regards,
Dennis

From: Scott, Kimberly [mailto:Kimberly.Scott@fda.hhs.gov]
Sent: Wednesday, March 25, 2015 3:55 PM
To: Dennis Williams; Ganeshan, Shanthi
Cc: Miller, Mara Bauman; Scott, Kimberly
Subject: NDA 207027 Promacta: Not met Electronic Submission Requirements for cross referencing previous submitted

information
Importance: High

Good afternoon Dennis,

This email is to inform GSK/Novartis that you did not meet electronic submission requirements for cross referencing previously submitted information.

Both applications (i.e. NDA 022291 and NDA 207027) are in eCTD format therefore, GSK/Novartis can apply cross application linking. Please see the general information I received below, regarding cross application linking.

General Information

To apply cross application links, both applications would need to be in eCTD format and resides on the same server (which is the case, for both applications).

The applications need to include the appropriate prefix in the href links (e.g. nda, ind). In the leaf titles of the documents, it is recommended that the leaf title indicate the word "cross reference to" and the application number (e.g. general-information-cross-ref-to-nda XXXXXX or something similar). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application.

Prior to using cross application linking in an application, it is recommended that sponsor submits an "eCTD cross application links" sample, to ensure successful use of cross application links.

To submit an eCTD cross application links sample, sponsor would need to request two sample application numbers from the ESUB team - esub@fda.hhs.gov .

For more information on eCTD sample, please refer to the Sample Process web page, which is located at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

If you need more information on cross application linking, you can contact esub@fda.hhs.gov.

Please confirm receipt of this email.

Thank you,
Kimberly
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
10903 New Hampshire Avenue, Bldg 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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/s/

KIMBERLY L SCOTT
03/27/2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Wednesday, March 25, 2015 3:55 PM
To: dennis.q.williams@gsk.com; Ganeshan, Shanthi
Cc: Miller, Mara Bauman; Scott, Kimberly (Kimberly.Scott@fda.hhs.gov)
Subject: NDA 207027 Promacta: Not met Electronic Submission Requirements for cross referencing previous submitted information

Importance: High

Good afternoon Dennis,

This email is to inform GSK/Novartis that you did not meet electronic submission requirements for cross referencing previously submitted information.

Both applications (i.e. NDA 022291 and NDA 207027) are in eCTD format therefore, GSK/Novartis can apply cross application linking. Please see the general information I received below, regarding cross application linking.

General Information

To apply cross application links, both applications would need to be in eCTD format and resides on the same server (which is the case, for both applications).

The applications need to include the appropriate prefix in the href links (e.g. nda, ind). In the leaf titles of the documents, it is recommended that the leaf title indicate the word "cross reference to" and the application number (e.g. general-information-cross-ref-to-nda XXXXXX or something similar). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application.

Prior to using cross application linking in an application, it is recommended that sponsor submits an "eCTD cross application links" sample, to ensure successful use of cross application links.

To submit an eCTD cross application links sample, sponsor would need to request two sample application numbers from the ESUB team - esub@fda.hhs.gov .

For more information on eCTD sample, please refer to the Sample Process web page, which is located at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

If you need more information on cross application linking, you can contact esub@fda.hhs.gov.

Please confirm receipt of this email.

Thank you,
Kimberly
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
10903 New Hampshire Avenue, Bldg 22, Rm 2222
Silver Spring, MD 20993

Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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/s/

KIMBERLY L SCOTT
03/25/2015

Scott, Kimberly

From: Scott, Kimberly
Sent: Monday, March 23, 2015 3:04 PM
To: 'Dennis Williams'
Subject: RE: NDA 207027 - FDA Information Request: Human Factors/Labeling studies?

Importance: High

Good afternoon Dennis,

In discussion with the team, your proposed final report for mid-late May does not provide sufficient time for review and evaluation of the study results to support the labeling of the product. As a result, we request you submit the HF study results by **Friday, April 24, 2015** in order to accommodate the prompt review of your Application.

In regards to the stick pack, I left a message on your voicemail. The Agency is requesting two samples.

Please confirm receipt of this email.

Regards,
Kimberly
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
10903 New Hampshire Avenue, Bldg 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Dennis Williams [mailto:dennis.q.williams@gsk.com]
Sent: Monday, March 23, 2015 9:55 AM
To: Scott, Kimberly
Subject: RE: NDA 207027 - FDA Information Request: Human Factors/Labeling studies?

Hi Kimberly,

Attached is the final human factors protocol. This protocol will be submitted to the NDA as well.

Regards,
Dennis

From: Scott, Kimberly [mailto:Kimberly.Scott@fda.hhs.gov]
Sent: Friday, March 20, 2015 7:41 PM
To: Dennis Williams
Subject: RE: NDA 207027 - FDA Information Request: Human Factors/Labeling studies?
Importance: High

Good evening Dr. Williams,

Thank you for responding to my request regarding NDA 207027 Promacta. If you've any additional information regarding human factors/usability study for the protocol that you've not yet submitted, please send it to me via email as well as to the NDA. I will inform the Agency that we can expect to receive your final report on human factors/usability study by mid-late May.

In addition, did you receive my email regarding the request for a sample of Powder for Oral Suspension Kit (i.e., stickpack packets, oral dosing syringe, reconstitution bottle, bottle lid) be sent to the Agency by April 6, 2015?

Please confirm receipt of this email.

Thank you,
Kimberly
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
10903 New Hampshire Avenue, Bldg 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Dennis Williams [mailto:dennis.g.williams@gsk.com]
Sent: Friday, March 20, 2015 2:03 PM
To: Scott, Kimberly
Subject: RE: NDA 207027 - FDA Information Request: Human Factors/Labeling studies?

Hi Kimberly,

A human factors/usability study is in progress; we expect the final report to be available in mid-late May.

Let me know if you want me to send any further details (protocol, etc.).

Thanks,
Dennis

From: Scott, Kimberly [mailto:Kimberly.Scott@fda.hhs.gov]
Sent: Friday, March 20, 2015 1:01 PM
To: Dennis Williams
Cc: Scott, Kimberly
Subject: NDA 207027 - FDA Information Request: Human Factors/Labeling studies?
Importance: High

Good afternoon Dr. Williams,

The Agency is requesting any human factors/usability or labeling comprehension studies for NDA 207027. Please send the information via email as well as formally submit to your NDA by 1:00pm on Monday, March 30, 2015.

Please confirm receipt of this email.

Thank you,
Kimberly
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service

Regulatory Health Project Manager
Division of Hematology Products|Office of Hematology and Oncology Products
Center for Drug Evaluation and Research|Food and Drug Administration
10903 New Hampshire Avenue, Bldg 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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/s/

KIMBERLY L SCOTT
03/23/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207027

NDA ACKNOWLEDGMENT

GlaxoSmithKline LLC
Attention: Dennis R. Williams, PharmD
Director, Global Regulatory Affairs, Oncology
1250 South Collegeville Road
Collegeville, PA 19426

Dear Dr. Williams:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Promacta® (eltrombopag), 25 mg (b) (4) for oral suspension

Date of Application: February 24, 2015

Date of Receipt: February 24, 2015

Our Reference Number: NDA 207027

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 25, 2015, in accordance with 21 CFR: 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR: 314.50(l)(1)(i) in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please call me at (240) 402-4560.

Sincerely,

{See appended electronic signature page}

Kimberly Scott, RN, BSN, OCN®
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

KIMBERLY L SCOTT
03/06/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 063293

MEETING PRELIMINARY COMMENTS

GlaxoSmithKline, LLC
Attention: Dennis Williams, Pharm.D
Director, Global Regulatory Affairs, Oncology
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426

Dear Dr. Williams:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Promacta (eltrombopag) Tablets.

We also refer to your March 25, 2014 correspondence, received March 25, 2014, requesting a meeting to discuss the content, format, and acceptability of the proposed sNDA in pediatric chronic ITP based on the results of the PETIT studies.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-0683.

Sincerely,

{See appended electronic signature page}

Mara Miller, MA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	Pre-sNDA
Meeting Date and Time:	May 22, 2014 1:00-2:00 PM
Meeting Location:	White Oak Building #22
Application Number:	IND 063293
Product Name:	Promacta (eltrombopag)
Indication:	Pediatric ITP
Sponsor/Applicant Name:	GlaxoSmithKline

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for May 22, 2014 between GSK and the Division of Hematology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 Sponsor Questions and FDA Responses

Question 1:
Does the Division agree the size of safety database in the pediatric chronic ITP population is acceptable for the proposed sNDA?

FDA Response
The size of the safety database appears to be acceptable.

Question 2:
GSK intends to submit complete Integrated Summaries of Effectiveness and Safety in module 5 in addition to the Summaries of Clinical Efficacy and Safety in module 2. Does the Division agree with GSK's proposal for the format for the Summary of Clinical Efficacy/Safety (SCE/SCS) and Integrated Summary of Efficacy/Safety (ISE/ISS)?

FDA Response
Yes.

Question 3:
Does the Division agree with GSK's proposal for submission of patient narratives and Case Report Forms (CRFs) for the PETIT studies?

FDA Response
Yes. If additional CRFs are needed, they will be requested.

Question 4:
Does the Division agree that the proposed format of the datasets is acceptable?

FDA Response
Yes, the proposal is acceptable. Please make sure base and final model control and output files are in .txt file type.

Question 5:
Given the CMC information related to eltrombopag olamine is (b) (4) approved under NDA 022291 for PROMACTA® (eltrombopag) tablets, GSK intends to cross-reference all drug substance information from NDA 022291. NDA 207027 will provide S.4.4 Batch Analyses_Non-clinical and Clinical_Eltrombopag Olamine for information relevant to Powder for Oral Suspension clinical studies. Is this approach acceptable to the Agency?

FDA Response
Yes, this approach is acceptable. However, in addition to the batch analyses update, provide in your NDA application a summary of all drug substance changes made since the approval of NDA 022291.

Additional Comment
Sponsors options of cross referencing information submitted to another application would be to either place a cross reference document under module m1.4.4 (cross reference to other applications), or use cross application links.

1. To use the first option (placing a cross reference document in m1.4.4), a table formatted document can be submitted in section 1.4.4 of the eCTD, detailing previously submitted information (eCTD and/or non- eCTD) that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), (5) the eCTD sequence number, (6) the eCTD heading location (e.g., m3.2.p.4.1 Control of Excipients – Specifications), (7) the document leaf title and (8) the submission identification (e.g., submission serial number, volume number, electronic folder, file name, etc,.,) of the referenced document along with a hypertext link to the location of the information, when possible.

2. To use the second option (cross application links), both applications would need to be in eCTD format and reside on the same server. The applications need to include the appropriate prefix in the href links (e.g. nda, ind,). Also, when cross application links are used, it's strongly recommended that a cross reference document be placed in m1.4.4, in case any of the links don't work and in the leaf titles of the documents, it is recommended that the leaf title indicate the word "cross reference" and application number (e.g. Cross Ref to nda123456). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application and the application number that is being referenced.

Prior to using cross application linking in an application, it is recommended that sponsor submits an "eCTD cross application links" sample, to ensure successful use of cross application links.

To submit an eCTD cross application links sample, sponsor would need to request two sample application numbers from the ESUB team - esub@fda.hhs.gov. For more information on eCTD sample, please refer to the Sample Process web page which is located at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

Question 6:
To fulfill the requirements regarding executed batch records for primary stability batches, GSK proposes submitting a single executed batch record for each drug product strength (Eltrombopag PfOS, (b) (4) 25 mg) in the NDA, with all batch records being available at the site or upon request. These primary stability batch records are representative of the proposed commercial process. Is this approach acceptable to the Agency?

FDA Response
No, this approach is not acceptable. Submit in your NDA application the batch record for the three primary stability batches made at the commercial site and commercial scale for both strengths of the drug product.

Question 7:
Does the Division agree the proposed application content/format is acceptable for submission of the proposed sNDA for the "*treatment of thrombocytopenia in adult and pediatric patients with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy*"?

FDA Response
Yes, we agree with the proposed content/format. The exact wording of the indication will be a review issue. Your clinical pharmacology and biopharmaceutics summaries should be comprehensive with new information clearly highlighted and "across study analysis" revised to include the new information where appropriate.

Question 8:
Does the Division agree the proposed application content/format is acceptable for submission of the proposed NDA for the PROMACTA powder for oral suspension formulation?

FDA Response
Yes.

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/s/

MARA B MILLER
05/19/2014

Reference ID: 3813450

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2/CMC
Meeting Date and Time:	March 22, 2012 1:00-2:00 PM(EST)
Meeting Location:	Teleconference
Application Number:	IND 063293
Product Name:	Eltrombopag Olamine (SB-497115-GR)
Indication:	Treatment of Thrombocytopenia
Sponsor/Applicant Name:	GlaxoSmithKline
Meeting Chair:	Sarah Pope Miksinski, PhD
Meeting Recorder:	Deborah Mesmer, MS

FDA ATTENDEES
Kareen Riviere, PhD, Pharmacologist, ONDQA
Yekena Maslov, PharmD, Pharmacologist, OSE
Gaetan Ladouceur, PhD, Chemist, ONDQA
Janice Brown, PhD, CMC Lead, ONDQA
Sarah Pope Miksinski, PhD, Branch Chief , ONDQA
Deborah Mesmer, MS, Regulatory Health Project Manager ONDQA
Sarah Vee, PharmD, Pharmacist, OSE
Sandra Suarez, PhD, Pharmacologist, ONDQA
Sue Kang, Regulatory Health Project Manager, OSE
Frances Fahnbulleh, Regulatory Health Project Manager, OSE

SPONSOR ATTENDEES
Frank Muller, PhD, Director, Product Development
Shiva Kapsi, PhD, Senior Scientific Investigator, Product Development
Esteban Bornancini, Senior Scientific Investigator, Product Development
Dale Stockbower, Director, Global Pre-Approval, CMC Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 063293

MEETING MINUTES

GlaxoSmithKline
Attention: Dale E. Stockbower, Director,
Global Pre-Approval CMC Regulatory Affairs
1250 South Collegeville Road, P.O. Box 5089
Collegeville PA 19426-0989

Dear Ms. Stockbower:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Eltrombopag Olamine (SB-497115-GR).

We also refer to the meeting between representatives of your firm and the FDA on March 22, 2012. The purpose of the meeting was to discuss the Quality section of your proposed NDA submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions call me at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Jewell D. Martin, MA, MBA, PMP
Regulatory Health Project Manager for Product Quality
Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

1.0 BACKGROUND

On January 20, 2012 GlaxoSmithKline, LLC (GSK) requested a Type B, CMC End-of-Phase 2 meeting to discuss the CMC development plan in support of an NDA submission for the Eltrombopag Powder for Oral Suspension (PfOS), to be held at the FDA White Oak campus.

The Office of New Drug Quality Assessment (ONDQA) sent GSK preliminary comments on March 19, 2012. As a result of the FDA comments GSK requested to change the meeting format to a teleconference and amend the agenda to focus the discussion on Questions 1, 2, 3 (bullet 3) and 4. GSK accepted the FDA's preliminary comments for Question 3 (bullets 1- 2 and 4-7), 5 and 6 and felt that there was no need further discussion required. In order to facilitate the meeting discussion, GSK submitted slides (see Section 6.0 – Attachments and Handouts) on March 21, 2012. At the request of Debbie Mesmer, Regulatory Health Project Manager, these slides were amended to include numbers for each slide (i.e. 1-12), and were submitted to the FDA on March 22, 2012. GSK responses (found in March 22, 2012 slides) to FDA Preliminary comments are integrated in the Discussion section (see Section 2.0 – Discussion) for convenience and also attached (see Section 6.0 – Attachments and Handouts) for reference.

2.0 DISCUSSION

Question 1:
Does the Agency agree that the proposed reconstitution procedure for commercial Eltrombopag Powder for Oral Suspension (PfOS), (b) (4) product is appropriate for Patient dosing and administration?

FDA Response:
It is unclear from your proposed reconstitution procedure for commercial Eltrombopag (b) (4) for Oral Suspension whether the consumers should (b) (4) add (b) (4) of water. It is not practical for consumer to add (b) (4) (b) (4) Ideally, if your drug product formulation permits, the Instructions for Use should not instruct consumers to use (b) (4) of water (b) (4) Instead, Instructions for Use should instruct the patients or their caregivers (b) (4) and add the contents of the (b) (4) We also recommend that the Instructions for Use should be tested in a comprehension study to ensure the end users understand the reconstitution procedure prior to marketing of the product.

Also, in order to simplify and avoid potential medication errors in the reconstitution process, we recommend that you (b) (4) of the Eltrombopag PfOS (b) (4)

GSK Response (March 22, 2012 Slides):

- GSK agrees that it is not practical for the consumer to add (b) (4) of water, and clarifies that the reconstitution procedure involves the addition of water by the consumer (b) (4) (b) (4) The Instructions for Use will clearly and accurately reflect the

reconstitution procedure that the consumer should follow, and a comprehension study prior to marketing will be considered to ensure end user understanding of the procedure.

- GSK recognizes that multiple prepackaged strengths may be of value. The strength(s) of Eltrombopag PfOS which will be proposed for commercial product will be determined based on data from the pivotal clinical studies.

Meeting Discussion Question 1: The Agency found the sponsor's proposal acceptable and recommended that the instructions for use comprehension study be submitted when/if completed.

Question 2:
Does the Agency agree that the data provided demonstrate acceptable equivalence between the (b) (4) used to manufacture pivotal clinical batches and the (b) (4) proposed to manufacture NDA stability batches and commercial batches of Eltrombopag PfOS, (b) (4)?

FDA Response:
No. The proposed change in the (b) (4) (b) (4) (b) (4) The analysis should be performed on the dry powder and the reconstituted product. A final determination of acceptability will be made during the NDA review.

Meeting Discussion Question 2: Applicant accepted FDA preliminary responses. No further discussion was needed.

Question 3:
Does the Agency agree that the analytical tests described in the proposed specification for Eltrombopag PfOS, (b) (4) and those tests that will be conducted for information are suitable (1) for testing the NDA stability batches and (2) to establish the appropriate tests for controlling the quality of commercial product?

FDA Response:
No. Your proposed drug product specification does not appear adequate.

- **Based on the proposed drug product specification (Table 7), testing for identification of the active ingredients uses HPLC (b) (4) As per (b) (4) is not regarded as being specific. Provide an additional method (specific or non-specific) to establish the identity of the active moiety.**
- **Include a test for description of the reconstitution solution in the proposed drug product specification.**

- **If your proposed product will be reconstituted and administered as a suspension, add dissolution testing to the specifications table of this drug product. However, it appears that the suspension (b) (4) (Table 13). Please provide additional information (b) (4) (b) (4) (b) (4) Also provide the timing (post reconstitution) of the intended (labeled) and practical drug administration.**
- **Your proposal to omit microbial limit testing as part of the commercial drug product specification needs to be fully justified in the NDA submission based on the stability data as well as an adequate demonstration of microbiological control for the manufacturing process.**
- **Continue testing (b) (4) pH, reconstitution time, viscosity and microbial limits as part of the testing strategy for the drug product, and include all pertinent data in the NDA.**
- **Provide data to demonstrate that the reconstituted solution conforms to the drug product specification.**
- **Provide in-use compatibility and stability data to support the intended clinical administration of your drug product.**

GSK response for FDA Response Bullet #3 (March 22, 2012 Slides):

- GSK has provided data on the percent of drug dissolved at (b) (4) (b) (4) The intended timing for administration is immediately after reconstitution. GSK believes that data (b) (4) supports this timing.

Meeting Discussion Question 3: Refer to FDA Response bullet 3 and GSK Response. The sponsor agreed to state in the label that the product will be administered immediately but not to exceed 30 minutes post- reconstitution. The agency confirmed that it will need additional data to support any administration that occurs beyond 30 minutes post-reconstitution. The Agency also confirmed that a dissolution specification would be needed since the proposed product is a suspension.

Question 4:
Does the Agency (1) agree that the proposed dissolution method is suitable for testing of the NDA stability batches and (2) have any comments about its potential suitability as the commercial method?

FDA Response:
We do not have sufficient information to determine the suitability of the proposed dissolution method at this time.

In addition to the information requested in our response to question 3, provide the following supportive information in an IND amendment and/or your NDA submission:

1. **data and justification supporting the selection of (b) (4) rpm paddle speed,**
2. **data supporting the selection of the type and amount of surfactant, and**
3. **data demonstrating the discriminating capability of the selected dissolution test.**

GSK Responses (March 22, 2012 Slides):

GSK Response to question 4.1 (see slides 5-6)

- As described in USP<1088> and <1092>, (b) (4) rpm is a common operating speed for the use of paddles in testing dissolution of suspensions, and speeds (b) (4) rpm or (b) (4) rpm are inappropriate due to inconsistency of hydrodynamics or turbulence, respectively
- Early development work on a dissolution method for Eltrombopag PfOS evaluated the paddle speeds of (b) (4) 50 rpm. The current proposed dissolution medium of potassium phosphate buffer pH 6.8 with (b) (4) %v/v polysorbate 80 was used. Dissolution profiles at all three paddle speeds were similar (as shown in the next slide).
- (b) (4)

** See graph on slide 6

GSK Response to question 4.2 (see slide 7)

- Type of Surfactant: Non-ionic surfactant Polysorbate 80 employed to develop the dissolution method because (b) (4)
  - Polysorbate 80 is the surfactant for the dissolution method employed for commercialized Eltrombopag (Promacta®) Tablets
- Amount of Surfactant: As described in the EoP2 briefing document, the surfactant concentrations (b) (4) v/v polysorbate 80.

GSK Response to question 4.3 (see slides 8-12)

- Eltrombopag PfOS is a dry powder blend in a (b) (4) reconstituted in water prior to dosing
  - If reconstituted as (b) (4) concentration depending on the dose
  - Eltrombopag olamine has a water solubility of (b) (4)
  - Assessment of solubility of Eltrombopag in the reconstituted suspension (b) (4) (b) (4)
- Eltrombopag pH-solubility profile:
  - Eltrombopag olamine exhibits typical solubility behavior (b) (4)
    - Poor solubility in acid media and an increase in solubility with increasing pH

- Low solubility in acidic to neutral pH buffers provided an opportunity to explore developing a dissolution method that would generate a profile.

- Irrespective of the media pH, buffer species, surfactant level and media volume; the rate of dissolution remained unchanged

(b) (4)

(b) (4)

- Conclusion:
  - Considering that the (b) (4) (b) (4) and variables such as pH, media volume, surfactant level and sample introduction only influenced the extent of dissolution and not the rate of dissolution, a dissolution method for Eltrombopag PfOS with a dissolution profile could not be generated, with the extensive evaluation performed to date.

Meeting Discussion Question 4: Sponsor committed to provide additional data to support either the discriminating ability of the dissolution method and/or the link between potential critical quality attributes, such as particle size, and clinical relevance. The Sponsor agreed to submit the data as an IND amendment, and the Agency committed to provide a written response within 30 days.

Question 5:
GSK intends to submit the NDA with 12 month stability data on three full scale drug product batches manufactured at commercial scale at the commercial site using the proposed commercial process. Will the Agency accept an 18 month stability update to be submitted at least 3 months prior to the action date in support of a 24 month expiry date, with no impact on the regulatory review timings?

FDA Response:
As per the Agency's 21st Century (GRMP) Initiative, all NDAs are to be complete in the original submission. Amendments submitted to an NDA subsequent to the original submission may or may not be reviewed as resources allow.

Meeting Discussion Question 5: Applicant accepted FDA preliminary responses. No further discussion was needed.

Question 6:
Does the Agency agree that the proposed stability protocols for Eltrombopag PfOS, (b) (4) are appropriate to support the NDA?

FDA Response: See response to question 3.

Meeting Discussion Question 6: Applicant accepted FDA preliminary responses. No further discussion was needed.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no specific issues requiring further discussion at this time.

4.0 ACTION ITEMS

There are no specific due dates or time lines for submission of information or other action items. General agreements and commitments are included in the Discussion section (2.0) above.

5.0 CONCURRENCE:

{See appended electronic signature page}

Jewell D. Martin, MA, MBA, PMP
Regulatory Health Project Manager for Product Quality
Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

{See appended electronic signature page}

Deborah Mesmer, MS
Regulatory Health Project Manager for Product Quality
Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

{See appended electronic signature page}

Sarah C. Pope Miksinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

6.0 ATTACHMENTS AND HANDOUTS

The attached slides were submitted by GSK to facilitate the discussion during the meeting. These slides are referred to in the Discussion Section (2.0) above.

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

/s/

JEWELL D MARTIN
04/20/2012

DEBORAH M MESMER
04/20/2012

SARAH P MIKSINSKI
04/20/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 063293

MEETING PRELIMINARY COMMENTS

GlaxoSmithKline
Attention: Dale E. Stockbower, Director,
Global Pre-Approval CMC Regulatory Affairs
1250 South Collegeville Road, P.O. Box 5089
Collegeville PA 19426-0989

Dear Ms. Stockbower:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for eltrombopag olamine (SB-497115-GR), (TPO Receptor Agonist).

We also refer to your January 20, 2012, correspondence requesting a meeting to discuss the Quality section of your proposed NDA submission.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the Type B End-of-Phase 2 meeting scheduled for March 22, 2012 between GlaxoSmithKline and the Office of New Drug Quality Assessment. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

CMC Questions:

Question 1:
Does the Agency agree that the proposed reconstitution procedure for commercial Eltrombopag Powder for Oral Suspension (PfOS), (b) (4) product is appropriate for Patient dosing and administration?

FDA Response:
It is unclear from your proposed reconstitution procedure for commercial Eltrombopag (b) (4) for Oral Suspension whether the consumers should (b) (4) (b) (4) add (b) (4) of water. It is not practical for consumer to add (b) (4) (b) (4) Ideally, if your drug product formulation permits, the Instructions for Use should not instruct consumers to use (b) (4) of water (b) (4) Instead, Instructions for Use should instruct the patients or their caregivers (b) (4) and add the contents of the (b) (4) We also recommend that the Instructions for Use should be tested in a comprehension study to ensure the end users understand the reconstitution procedure prior to marketing of the product.

Also, in order to simplify and avoid potential medication errors in the reconstitution process, we recommend that you (b) (4) of the Eltrombopag PfOS (b) (4)

Question 2:
Does the Agency agree that the data provided demonstrate acceptable equivalence between the (b) (4) used to manufacture pivotal clinical batches and the (b) (4) proposed to manufacture NDA stability batches and commercial batches of Eltrombopag PfOS, (b) (4)?

FDA Response:
No. The proposed change in the (b) (4) (b) (4) (b) (4) The analysis should be performed on the dry powder and the reconstituted product. A final determination of acceptability will be made during the NDA review.

Question 3:
Does the Agency agree that the analytical tests described in the proposed specification for Eltrombopag PfOS, (b) (4) and those tests that will be conducted for information are suitable (1) for testing the NDA stability batches and (2) to establish the appropriate tests for controlling the quality of commercial product?

FDA Response:
No. Your proposed drug product specification does not appear adequate.

- **Based on the proposed drug product specification (Table 7), testing for identification of the active ingredients uses HPLC (b) (4) As per (b) (4) is not regarded as being specific. Provide an additional method (specific or non-specific) to establish the identity of the active moiety.**
- **Include a test for description of the reconstitution solution in the proposed drug product specification.**
- **If your proposed product will be reconstituted and administered as a suspension, add dissolution testing to the specifications table of this drug product. However, it appears that the suspension (b) (4) (Table 13). Please provide additional information (b) (4) (b) (4)**
- **Your proposal to omit microbial limit testing as part of the commercial drug product specification needs to be fully justified in the NDA submission based on the stability data as well as an adequate demonstration of microbiological control for the manufacturing process.**
- **Continue testing (b) (4) pH, reconstitution time, viscosity and microbial limits as part of the testing strategy for the drug product, and include all pertinent data in the NDA.**
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Question 4:
Does the Agency (1) agree that the proposed dissolution method is suitable for testing of the NDA stability batches and (2) have any comments about its potential suitability as the commercial method?

FDA Response:
We do not have sufficient information to determine the suitability of the proposed dissolution method at this time.

In addition to the information requested in our response to question 3, provide the following supportive information in an IND amendment and/or your NDA submission:

1. **data and justification supporting the selection of (b) (4) rpm paddle speed,**
2. **data supporting the selection of the type and amount of surfactant, and**
3. **data demonstrating the discriminating capability of the selected dissolution test.**

Question 5:
GSK intends to submit the NDA with 12 month stability data on three full scale drug product batches manufactured at commercial scale at the commercial site using the proposed commercial process. Will the Agency accept an 18 month stability update to be submitted at least 3 months

prior to the action date in support of a 24 month expiry date, with no impact on the regulatory review timings?

FDA Response:
As per the Agency's 21st Century (GRMP) Initiative, all NDAs are to be complete in the original submission. Amendments submitted to an NDA subsequent to the original submission may or may not be reviewed as resources allow.

Question 6:
Does the Agency agree that the proposed stability protocols for Eltrombopag PfOS, (b) (4) are appropriate to support the NDA?

FDA Response: See response to question 3.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call Jewell Martin, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Jewell Martin, MA, MBA, PMP
Senior Regulatory Health Project Manager for Quality
Food and Drug Administration
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

Sarah C. Pope Miksinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

JEWELL D MARTIN
03/19/2012

SARAH P MIKSINSKI
03/19/2012