CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204958Orig1s000

<u>OTHER REVIEW(S)</u>

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Review

NDA:	204958
Drug:	KENGREAL (cangrelor) for injection
Class:	$P2Y_{12}$ Platelet Inhibitor
Applicant:	The Medicines Company
Proposed Indication:	[redacted] (b) (4) is an intravenous $P2Y_{12}$ platelet inhibitor indicated for the reduction of thrombotic cardiovascular events in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) [redacted] (b) (4) (b) (4) [redacted] KENGREXAL significantly reduced the primary composite endpoint of all-cause mortality, myocardial infarction (MI), ischemia driven revascularization (IDR), and stent thrombosis (ST) compared to clopidogrel. The difference between treatments was driven by reductions in peri-procedural MI and ST with no difference in all-cause mortality *[see Clinical Studies (14.1)]*.
<u>FINAL</u> Indication:	KENGREAL is indicated as an adjunct to percutaneous coronary intervention (PCI) to reduce the risk of periprocedural myocardial infarction (MI), repeat coronary revascularization, and stent thrombosis (ST) in patients who have not been treated with a $P2Y_{12}$ platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor *[see Clinical Studies (14.1)]*.
Date of Re-submission:	23 December 2014
Approval date:	22 June 2015
PDUFA date:	23 June 2015

- **REVIEW TEAM**
  - Office of New Drugs, Office of Drug Evaluation I (ODE I)
    - Signatory Authority, ODE I
      - Robert Temple, M.D. (Deputy Office Director)
    - Division of Cardiovascular & Renal Products (DCRP)
      - Norman Stockbridge, M.D., Ph.D. (Division Director)
      - Stephen Grant, M.D. (Cycle #2 - Cross-Discipline Team Leader - CDTL)
      - Thomas Marciniak, M.D. (Cycle #1 - Cross-Discipline Team Leader - CDTL)
      - Fred Senatore, M.D., Ph.D. (Clinical Reviewer - Efficacy)

        - Nhi Beasley, PharmD (Clinical Reviewer – Safety)
        - Belay Tesfamariam, Ph.D. (Pharmacology-Toxicology)
        - Alison Blaus, RAC (Senior Regulatory Health Project Manager)
    - Office of Clinical Pharmacology
        - Sreedharan Sabarinath, Ph.D.
    - Office of Biostatistics, Division of Biometrics I
        - Jialu Zhang, Ph.D.
    - Office of Product Quality (OPQ)
        - Wendy Wilson, Ph.D. (OPQ Overview Review)
        - David Claffey, Ph.D. (Cycle #1 - Drug Substance / Drug Product)
        - Okpo Eradiri, Ph.D. (Cycle #2 - Biopharmaceutics)
        - Kareen Riviere, Ph.D. (Cycle #1 - Biopharmaceutics)
        - Steven Donald, Ph.D. (Microbiology)
    - Office of Surveillance and Epidemiology
        - Kimberly Defronzo, RPh, MS, MBA (DMEPA – Tradename Review)
        - Loretta Holmes (DMEPA – Tradename Review)
        - Janine Stewart, PharmD (DMEPA – Tradename/Labeling Review)
        - Tingting Gao (DMEPA – Labeling Review)
        - Kimberly Lehrfield, PharmD (DRISK Team Leader)
        - Somya Dunn, M.D (DRISK Reviewer)
    - Office of Medical Policy
        - Office of Prescription Drug Promotion (OPDP)
            - Zarna Patel – Patient Labeling
        - Patient Labeling
            - Karen Dowdy, RN, BSN (Medication Guide)

❖ BACKGROUND

KENGREAL (cangrelor) for injection is a reversible inhibitor of the platelet $P2Y_{12}$ receptor and has a mechanism of action different from ticagrelor. The Medicines Company (TMC) developed cangrelor for the following indications:

PCI

Cangrelor for injection is an intravenous (IV) $P2Y_{12}$ platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI). In CHAMPION PHOENIX, cangrelor significantly reduced (relative risk reduction [RRR] 22%) the primary composite endpoint of all-cause mortality, myocardial infarction (MI), ischemia driven revascularization (IDR), and stent thrombosis (ST) compared to clopidogrel.

Bridging

Cangrelor for injection is indicated to maintain $P2Y_{12}$ inhibition in patients with acute coronary syndromes (ACS) or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery.

TMC submitted a new drug application (NDA 204948) with the clinical trial data (CHAMPION PCI, CHAMPION PLATFORM, CHAMPION PHOENIX, & BRIDGE) to support these indications on

30 April 2013. This PDUFA V application was reviewed under "The Program". Upon review of the clinical data and a related Advisory Committee Meeting (ADCOM) on 12 February 2014, a Complete Response (CR) letter was issued on 30 April 2014.

After the CR letter was issued, a meeting was scheduled for 5 August 2014 to discuss the applicant's plan to address the CR Letter and to obtain feedback from the Agency on whether their plan would constitute a complete response to our 30 April 2014 letter. These discussions were captured in the minutes dated 9 September 2014.

On 23 December 2014, TMC resubmitted the NDA (Acknowledged as a Class II resubmission).

❖ REGULATORY TIMELINE and GENERAL APPLICATION MILESTONES

This section will cover a number of clinical development and general application milestones (pre- and post-NDA submission). The review of this application proceeded relatively smoothly, with approximately 73 information requests since 30 April 2013.

- IND received: 20 August 1998
- End of Phase 2 Meeting for CHAMPION PCI/PLATFORM: 6 July 2005 (minutes dated 4 August 2005)
- There was no SPA for CHAMPION-PHOENIX
- Pre-NDA Meetings:
  - 20 November 2012 BRIDGE (minutes dated 26 December 2012)
- Top-Line Meetings:
  - 9 November 2009 CHAMPION PCI/PLATFORM (minutes dated 30 November 2009)
  - 14 May 2012 BRIDGE (minutes dated 8 June 2012)
  - 15 August 2012 BRIDGE Follow-up (minutes dated 12 September 2012)
  - 25 February 2013 CHAMPION PHOENIX (minutes dated 3 April 2013)
- NDA Submission Received: 30 April 2013
- Filing Date (Day 60): 29 June 2013
- 74-day Issues Letter with Comments: 13 July 2013
- Mid-Cycle Meeting: 7 October 2013
- Mid-Cycle Communication Meeting: 21 October 2013 (minutes dated 13 November 2013)
- Late-Cycle Briefing Book Finalized: 21 January 2014
- Late-Cycle Communication Meeting: 29 January 2014 (minutes dated 28 February 2014)
- Advisory Committee Meeting: 12 February 2014
- Post Advisory Committee Meeting: 4 March 2014 (minutes dated 14 April 2014)
- **Complete Response (CR): 30 April 2014**
- PDUFA Date: 30 April 2014
- Post-CR Meeting: 5 August 2014 (minutes dated 9 September 2014)
- NDA Resubmission: 23 December 2014
- Advisory Committee Meeting: 15 April 2015
- **Approval Date**: **22 June 2015**
- PDUFA Date: 23 June 2015

User Fee

The user fee for this application was paid in full on 15 April 2013, prior to the initial submission of the application (ID 3013265).

Pediatric Review Committee (PeRC)
The PeRC meeting to discuss this application was held on 20 November 2013. The applicant proposed a full waiver because coronary artery disease is extremely rare in the pediatric population. The PeRC and the Division agreed with the applicant's rationale. Therefore, a full pediatric waiver was granted for this application. In addition, we all agreed to include the applicant's proposed language which is consistent with 21 CFR 201.57 - "Safety and effectiveness in pediatric patients have not been established".

Advisory Committee
It was decided at the filing meeting and through internal discussions with various individuals within the Agency that an Advisory Committee (ADCOM) would be needed for this application.
After being presented the data (from both the applicant and the Agency) and engaging in multiple discussion topics, when asked, "Should cangrelor be approved for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing PCI?" the committee voted 2 (yes) to 7 (No). The committee members who voted "No" indicated concern about the design of CHAMPION and about the two earlier negative trials (PLATFORM and PCI), and felt that the increased risk of bleeding was not outweighed by the small clinical benefit.

As discussed at the 5 August 2014 post-CR meeting with the applicant, a second ADCOM was needed upon cangrelor's resubmission and it was held on 15 April 2015. This second meeting discussed issues raised at the first ADCOM as well as the issues that were highlighted in the April 2014 CR letter. At this second ADCOM, the members voted 9-2 in favor cangrelor's approval.

Please see the Agency's quick minutes from these meetings for a summary of each discussion question as well as the official transcript.

Trade name
A number of trade names were received and reviewed by DMEPA during the NDA review:

- 31 July 2013 – (b) (4) Trade name denied (Review dated 31 July 2013)
- 8 October 2013 – (b) (4) Trade name denied (Review dated 7 October 2013)
- 8 January 2014 – (b) (4) Trade name denied (Review dated 6 January 2014)
- 29 March 2014 – "KENGREAL" Trade name accepted (Review dated 25 March 2014)

Review Status
Due to the Phase 3 trial results from CHAMPION PHOENIX, and in light of the previous failed Phase 3 trials (CHAMPION-PCI and CHAMPION-PLATFORM), the applicant was granted a standard review.

❖ DISCIPLINE REVIEWS

Below are the conclusions reached by the Deputy Division Director and Deputy Office Director. Please refer to the individual discipline reviews for the primary reviewer's conclusions as well as those reviews completed prior to the 30 April 2014 Complete Response Letter.

Office Memorandum (22 June 2015)
Dr. Temple finalized a memo on 22 June 2015 concurring with Dr. Grant and the primary clinical reviews in recommending an approval for cangrelor. There was only one difference in opinion between Dr. Temple and Grant, and that difference was regarding the inclusion of the supplemental endpoint analyses in Section 14 of labeling (Clinical Studies).

Divisional Memorandum (19 June 2015)
Dr. Grant drafted and finalized a review from the Division on 19 June 2015 concurring with the primary clinical reviewers recommending approval.

❖ CONSULT REVIEWS

Please see the following consults that were requested during the NDA review and the corresponding date they were finalized:

- OSI (Clinical Audit): 29 April 2014 and 3 March 2015
- OSI (Bioequivalence Audit): n/a
- DMEPA (Trade name): see above Trade Name Section under Regulatory Timeline and General Application Milestones
- DMEPA (Carton-Container Labeling): 20 March 2014 and 24 February 2015
- DRISK (REMS): 21 January 2014
- Patient Labeling (Medication Guide): n/a (no Medication Guide)
- Office of Prescription Drug Promotion (OPDP): 10 June 2015

❖ CONCLUSION

After taking into consideration all of the primary reviews, consults, and the applicant's additional analyses, the Agency issued an approval letter for NDA 204958 (signed by Dr. Robert Temple) on 22 June 2015.

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

/s/

ALISON L BLAUS
06/22/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: June 10, 2015

To: Alison Blaus, RAC
Senior Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCRP)

From: Zarna Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **Kengreal (cangrelor) for injection, for intravenous use**
NDA: 204958
Comments on draft product labeling

OPDP has reviewed the proposed Package Insert (PI) submitted for consult on May 27, 2015, for Kengreal (cangrelor) for injection, for intravenous use (Kengreal). OPDP's comments are provided directly on the attached copy of the substantially complete PI emailed to us on May 27, 2015.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions, please contact Zarna Patel at 301.796.3822 or zarna.patel@fda.hhs.gov.

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

Reference ID: 3777016

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

/s/

ZARNA PATEL
06/10/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 24, 2015
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 204958
Product Name and Strength:	Kengreal (cangrelor) for Injection, 50 mg per vial
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	The Medicines Company
Submission Date:	March 26, 2014 December 23, 2014
OSE RCM #:	2015-254
DMEPA Primary Reviewer:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

Reference ID: 3706556

1 REASON FOR REVIEW

As a part of NDA 204958 Class 2 Resubmission, this review evaluates the proposed container labels, carton labeling, and Prescribing Information (PI) for areas of vulnerability that could lead to medication errors.

1.1 APPLICATION HISTORY

We previously reviewed Kengreal container labels, carton labeling, and PI[1], our recommendations for the container label and carton labeling were sent to the Applicant on March 21, 2014. In response to our previous recommendations, the Applicant provided revised container label and carton labeling on March 26, 2014. These revised container label and carton labeling were not reviewed by DMEPA at the time because NDA 204958 received a Complete Response on April 30, 2014. Additionally, our previous recommendations for the PI were not implemented.

On December 23, 2014, the Applicant submitted revised PI for their Class 2 Resubmission in response to Complete Response Letter. They did not submit a new container label and carton labeling in their resubmission.

Therefore, we evaluated the revised container label and carton labeling that were submitted on March 26, 2014 from the last review cycle and evaluated the proposed PI submitted on December 23, 2014.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B – N/A
Previous DMEPA Reviews	C
Human Factors Study	D – N/A
ISMP Newsletters	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

[1] Stewart J. Label and Labeling Review for Kengreal (NDA 204958). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 MAR 20. 31 p. OSE RCM No.: 2013-1169.

Reference ID: 3706556

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The revised container label and carton labeling are acceptable from a medication error perspective. The proposed prescribing information (PI) is unacceptable from a medication error perspective because our previous recommendations were not implemented. We notice the use of abbreviation 'IV' throughout the PI and recommend to replace the abbreviation 'IV' with their intended meaning (e.g. 'intravenous') to prevent misinterpretation and confusion.

Additionally, the proprietary name in the PI should be revised to the conditionally approved proprietary name (e.g. Kengreal instead of (b) (4)).

4 CONCLUSION & RECOMMENDATIONS

The March 26, 2014 revised container label and carton labeling are acceptable from a medication error perspective. The December 23, 2014 proposed prescribing information (PI) is unacceptable from a medication error perspective because our previous recommendations were not implemented. We provide specific recommendations for the PI in Section 4.1

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information (PI)

a. Kengreal represents the conditionally approved proprietary name for this proposed drug product. Therefore, replace (b) (4) with KENDGREAL throughout the PI.

b. Replace the abbreviation 'IV' with its intended meaning (e.g. 'intravenous') throughout the PI to prevent misinterpretation and confusion.

c. The abbreviation "µg" is listed as an error-prone abbreviation and may be misinterpreted as "mg".[2] Therefore, we recommend you to revise the abbreviation "µg" to "mcg" throughout the PI.

B. Dosage and Administration Section of Full PI

a. We recommend the following revision to improve clarity:

Original	Recommended revision
(b) (4)	Initiate KENDGREAL as a 30 mcg/kg intravenous bolus infusion prior to the procedure, followed immediately by a 4 mcg/kg intravenous infusion for at least 2 hours or for the entire duration of the procedure, whichever is longer.

[2] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2015 FEB 12]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

Reference ID: 3706556

C. How Supplied/Storage and Handling Section of Full PI

a. Update this section to state that Kengreal is supplied in carton of ten 10 mL single use vials, and to include the NDC number for each packaging configuration to ensure that this information is readily available in the PI.

Reference ID: 3706556

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Kengreal that The Medicines Company submitted on December 23, 2014.

Table 2. Relevant Product Information for Kengreal	
Initial Approval Date	N/A
Active Ingredient	Cangrelor
Indication	Reduction of thrombotic cardiovascular events in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) (b) (4)
Route of Administration	Intravenous
Dosage Form	Powder, for (b) (4)
Strength	50 mg per vial
Dose and Frequency	30 µg/kg intravenous bolus followed immediately by a 4 µg/kg/min intravenous infusion. The bolus infusion should be initiated prior to the procedure and continued for at least 2 hours or the duration of the procedure, whichever is longer. At the discretion of the physician, the infusion may be continued for a total duration of 4 hours.
How Supplied	Carton of 10 vials
Storage	20°C to 25°C (68°F to 77°F)
Container Closure	Single use 10 mL vial

Reference ID: 3706556

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:drive on February 9, 2014 using the terms, cangrelor to identify reviews previously performed by DMEPA.

C.2 Results

Our search identified one previous review[3], and we confirmed that our previous recommendation for the container label and carton labeling were implemented. However, our recommendations for the prescribing information were not implemented.

Therefore, we evaluated our previous recommendations for the prescribing information and noted that some of our previous recommendations (e.g. remove trailing zeros and organizing the dilution instructions for PCI (b) (4) in a table format to improve clarity) are no longer applicable to this review. Therefore, we repeated only the recommendations (e.g. replace the abbreviation 'IV' with the word 'intravenous') that are still applicable in this review.

[3] Stewart J. Label and Labeling Review for Kengreal (NDA 204958). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 MAR 20. 31 p. OSE RCM No.: 2013-1169.

Reference ID: 3706556

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[4] along with postmarket medication error data, we reviewed the following Kengreal labels and labeling submitted by The Medicines Company on March 26, 2014.

- Container label submitted on March 26, 2014
- Carton labeling submitted on March 26, 2014
- Prescribing Information submitted on December 23, 2014

G.2 Label and Labeling Images

Container Label (submitted on March 26, 2014)

(b) (4)

Carton labeling (submitted on March 26, 2014)

(b) (4)

[4] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Reference ID: 3706556

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

/s/

TINGTING N GAO
02/24/2015

CHI-MING TU
02/24/2015

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: April 29, 2014

TO: Fred Senatore, Medical Officer
Nhi Beasley, Clinical Safety Reviewer
Alison Blaus, Regulatory Project Manager
Division of Cardio-Renal Drug Products

FROM: Sharon K. Gershon, Pharm. D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Team Leader/Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 204958

APPLICANT: Medicines Company

DRUG: (b) (4) (cangrelor for injection)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: reduce thrombotic complications of Percutaneous Coronory Intervention in the acute setting

Protocol TMC-CAN-10-01: A Clinical Trial Comparing Cangrelor to Clopidogrel Standard of Care Therapy in Subjects Who Require Percutaneous Coronary Intervention (PCI):

CHAMPION PHOENIX: **Cangrelor versus standard therapy to achieve optimal management of platelet inhibition.**

CONSULTATION REQUEST DATE: June 25, 2013

INSPECTION SUMMRY GOAL DATE: February 28, 2014

ADVISORY COMMITTEE January 14, 2014

DIVISION ACTION GOAL DATE: April 29, 2014

PDUFA DATE: April 29, 2014

I. BACKGROUND:

The Medicines Company submitted NDA 204958 to market cangrelor for injection, in patients requiring percutaneous coronary intervention (PCI), (b) (4) There are several $P2Y_{12}$ inhibitors currently available including the thienopyridines ticlopidine, clopidogrel, and prasugrel. Limitations to this class of drugs include relatively slow onset of action, and by limited and variable on-treatment effect. Currently available agents are not useful in patients who cannot take them orally or absorb them. The sponsor claims that cangrelor is a parenteral $P2Y_{12}$ receptor inhibitor that rapidly and reversibly blocks platelet activation and aggregation. The sponsor claims that cangrelor has an immediate onset and a predictable and titratable antiplatelet effect which is more rapidly reversible than that of any approved $P2Y_{12}$ inhibitor. A brief description of the protocol follows.

Protocol TMC-CAN-10-01: A Clinical Trial Comparing Cangrelor to Clopidogrel Standard of Care Therapy in Subjects Who Require Percutaneous Coronary Intervention: CHAMPION PHOENIX: Cangrelor versus standard therapy to achieve optimal management of platelet inhibition.

This was a randomized, double-blind, parallel-group, superiority study of cangrelor efficacy compared with clopidogrel standard, and was conducted at 153 study centers in 12 countries: Austria, Brazil, Bulgaria, the Czech Republic, Georgia, Germany, Italy, New Zealand, Poland, Russia, Thailand, and the United States, between September 2010 and November 2012. The primary objective of the study was to demonstrate that in patients requiring PCI, cangrelor provides superior efficacy to clopidogrel standard of care, as measured by a composite of all-cause mortality, myocardial infarction (MI), ischemia-driven revascularization, and stent thrombosis. The main safety objective and secondary objective was to demonstrate that cangrelor has an acceptable safety profile without excessive peri-procedural bleeding as measured by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Trial (GUSTO) scale compared to the standard of care.

The following inclusion criteria must have been met: subjects at least 18 years of age with stable angina (SA), non-ST-segment elevation acute coronary syndrome (NSTE-ACS) and ST-segment elevation myocardial infarction (STEMI) who required PCI and had not previously received a $P2Y_{12}$ inhibitor within seven days. Key exclusion criteria include impaired hemostasis, severe uncontrolled hypertension, or increased bleeding risk. Screening for all subjects included angiography except STEMI subjects, for whom ECG criteria were sufficient. Patients were randomized 1:1 to receive either cangrelor infusion (Arm A, 30 ug/kg IV bolus followed by a 4 ug/kg/minute IV infusion continued for at least two hours or until the conclusion of the index procedure) or matching placebo infusion (Arm B), initiated post angiography but prior to the index PCI. At the time of PCI, as by standard of care, subjects then received their first set of capsules containing either clopidogrel (Arm B) or matching placebo (Arm A). At the end of the infusion, subjects received a second set of capsules containing either clopidogrel (Arm A) or matching placebo (Arm B). Subjects were assessed for the occurrence of efficacy endpoints at 48 hours and 30 + 5 days after randomization. Safety information was assessed at 48 hours. The maximum duration of a subject's participation was approximately 35 days. The primary efficacy endpoint was the composite incidence of all-cause mortality, MI, IDR, and stent thrombosis, assessed 48 hours after randomization.

Rationale for Site Selection
Cangrelor for injection is a NME with the proposed indication of reducing thrombotic complications of PCI in the acute setting. The site selection was based on the review division's analysis of efficacy. For this NDA, four foreign and one domestic site were chosen for inspections. Sites selected had high enrollment and significant primary efficacy results.

II. RESULTS

Name of CI/Address	Protocol # and # of Subjects	Inspection Dates	Final Classification
Tamaz Shaburishvili Tbilisi Heart & Vascular Clinic 18/20 Ljubljana Street Tbilisi, Georgia 0159	TMC-CAN-10-01 Site #495005 631 subjects	October 7 – 11, 2013	NAI
George Khabeishvili Diagnostic Services Clinic LTD 36, Ljubljana Street Tbilisi, Georgia 0159	TMC-CAN-10-01 Site #495002 325 subjects	October 14 – 16, 2013	NAI
Frantisek Tousek Nemocnice Ceske Budejovice, a.s. Dept Cardiology, B. Nemcove 585/54 Ceske Budejovice, Czech Republic	TMC-CAN-10-01 Site #420009 1064 subjects	October 21 – 25, 2013	VAI

Clemens Steinwender (formerly Franz Leisch) AKH Linz 1. Med. Abteilung, Krankenhausstrasse 9 Linz, Austria	TMC-CAN-10-01 Site #443002 539 subjects	October 14 – 17, 2013	NAI
Douglas Spriggs Clearwater Cardiovascular and Interventional Consultants 455 Pinellas Street, Suite 400 Clearwater, FL	TMC-CAN-10-01 Site #401030 365 subjects	September 23 – 27, 2014	NAI

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **Tamaz Shaburishvili**
Tbilisi Heart & Vascular Clinic, 18/20 Ljubljana Street
Tbilisi, Georgia 0159

a. What was inspected: This inspection was conducted according to Compliance Program 7348.811. Dr. Tamaz Shaburisvili has (b) (4) INDs in CDER's COMIS database, and no prior FDA inspection. At this site, 632 subjects were screened and 631 subjects randomized. The first subject was screened and entered the study on March 25, 2011; the last subject was screened and entered the study on October 2, 2012. Subject 317 was not randomized and a reason was not reported in the screening log.

A total of 133 subject files were reviewed – 57 were randomly selected and 76 were selected because of reported adverse events, protocol deviations, or other discrepancies noted during regulatory document review.

The following items were reviewed: Informed Consent Documents, inclusion and exclusion criteria, randomization, (b) (4) reports, uploading of angiogram/PCI films, end of study documents, 48- hour and 30- day follow-up visits, IVRS confirmation, drug accountability records, and patient history. Subject files included copies of ECGs and laboratory results. Documents were predominantly in Georgian, and a translator was present during the inspection to facilitate review of documents.

b. General observations/commentary: The FDA field investigator reported

that subject files were well-organized, readily available, and comprehensive. Minor recordkeeping deficiencies were observed: Subject 001 study completion page lacked subject number; Subject 003 randomization worksheet was not signed; Subject 076 end- of- study form was not fully completed (box was not checked "yes" for completion of study): four subjects (074, 180, 300, 524) had inconsistencies in their DOB information; and several subjects had incorrect initials.

The site used hard copy documentation. Information from the hard copy files were entered into the electronic case report forms (eCRFs). No discrepancies were found between the sponsor's data listings and the source documents. No instances of failing to report adverse events were observed. All endpoint data was verifiable.

During the inspection, the FDA field investigator asked about intra-procedural stent thrombosis (IPST), as requested by the review division. A representative from the sponsor present during the inspection said that all instances would have been determined by the cardiac adjudication committee, following review of PCI films. The FDA field investigator stated only that all instances of IPST were reported, but did not provide a number of IPST events.

c. **Assessment of data integrity:** In general, only very minor recordkeeping discrepancies were found during this inspection. These items were discussed with staff at the conclusion of the inspection and no Form FDA 483 was issued. These errors were isolated and minor and unlikely to significantly affect the integrity of the data. The study was conducted well at this site, and OSI recommends that the data are acceptable in support of the claimed indication

2. **George Khabeishvili**
Diagnostic Services Clinic LTD, 36, Ljubljana Street
Tbilisi, Georgia 0159

a. **What was inspected:** This inspection was conducted according to Compliance Program 7348.811. Dr. George Khabeishvili has (b) (4) INDs in CDER's COMIS database, and no prior FDA inspections. At this site, 325 subjects were screened and 325 subjects randomized. The first subject was screened and administered study drug on March 23, 2011. The last subject was screened and administered study drug on October 3, 2012.

A total of 80 subject files were reviewed – 54 were randomly selected and 26 were selected because of reported adverse events, protocol deviations or other discrepancies noted during regulatory document review. Subject files were reviewed for: Informed Consent signature dates, inclusion and exclusion criteria, randomization, (b) (4) reports, uploading of angiogram/PCI films, end of study documents, 48- hour and 30- day follow-up visits, IVRS confirmation, drug accountability records, and patient history. Subject files

included copies of ECGs and laboratory results. Documents were predominantly in Georgian, and a translator was present during the inspection to facilitate review of documents.

b. General observations/commentary: The FDA field investigator reported that subject files were well-organized, readily available and comprehensive. Review of 80 subject files found minor record keeping deficiencies:

- Subjects 025, 026, 027 had the incorrect angiogram/PCI films uploaded initially; this was corrected during the study, and the correct films verified during the inspection;
- Subjects 070 and 071 had mislabeled uploaded angiogram films initially: 070 films were uploaded as 071, and vice versa. This same finding was also identified for Subjects 188 and 189. These errors were corrected during the study.
- Subject 153 was identified with two different DOBs: (b) (6) and (b) (6). The correct DOB was confirmed as (b) (6).
- Subject 176 was identified with initials (b) (6); correct initials were confirmed as (b) (6)
- The 30-day follow-up visit/call record was not signed for Subject 117.

The site used hard copy documentation. Information from the hard copy files were entered into the electronic case report forms (eCRFs). No discrepancies were found between the sponsor's data listings and the source documents. No instances of failing to report adverse events, or serious adverse events were observed. All endpoint data was verified, there were no discrepancies. All protocol deviations were appropriately reported.

No reference to IPST was found during review of patient histories. Review of sponsor data found that the cardiac adjudication process was used to lead to a classification of IPST based upon review of PCI films.

c.Assessment of data integrity: In general, a few minor recordkeeping discrepancies were found during this inspection. These items were discussed with staff at the conclusion of the inspection and no Form FDA 483 was issued. The study was conducted well at this site, and OSI recommends that the data are acceptable in support of the claimed indication.

3. **Frantisek Tousek**
Nemocnice Ceske Budejovice, Dept Cardiology, B. Nemcove 585/54
Ceske Budejovice, Czech Republic 37087

a. What was inspected: This inspection was conducted according to Compliance Program 7348.811.Dr. Frantisek Tousek has (b) (4) INDs in COMIS database, and has had no prior inspections. At this site, 1064 subjects were enrolled. A total of 16 subjects did not meet the inclusion and exclusion criteria.

There were no instances of subjects withdrawing. Death was the only reason for a subject not completing the study. Eight deaths were reported and confirmed during the inspection. The first subject was screened, signed the informed consent document, and administered study drug on August 7, 2011. The last subject was screened and administered study drug on October 3, 2012.

A total of 230 subject files were reviewed. Of these, 189 were randomly selected and 34 selected based on associated adverse events, protocol deviations, or other discrepancies noted during regulatory file review.

Records were reviewed for IC date to ensure no study procedures were performed prior to signature; inclusion and exclusion criteria were met, randomization was appropriately done; (b) (4) reports were present; uploading of angiogram/PCI films were done, end-of-study documentation, 48 hour and 30-day follow-up done, IVRS confirmation and patient history present. Subject files also included copies of ECGs and laboratory results. The documents were written predominately in Georgian, and translated predominately by a sponsor CRO representative during the inspection.

b. **General observations/commentary:** Subject records were reported to be well-organized, readily available, and comprehensive. For the 230 subject files reviewed, the FDA noted minor record keeping deficiencies:

- Subject 005 was missing DOB on (b) (4) lab form
- Subject 010 had a 30-day follow-up date of 8/12 on the form whereas the subject was last treated on 8/11. The correct 30-day follow-up date should have been 9/12.
- Subject 717 was missing DOB, initials, and gender on the (b) (4) lab form
- Subject 919 did not have their 48-hour form completed
- Subject 988 had month of birth as (b) (6) on (b) (4) lab form – the correct month was (b) (6)
- Subject 1048 was missing gender on (b) (4) lab form.

The FDA field investigator reviewed records and confirmed two instances of an ineligible subject being enrolled, as reported by sponsor's data listings. Subject 439 had a hemoglobin level of 8.7 g/dL and Subject 1004 had a hemoglobin level of 9.2 g/dL. These were minor violations. A third ineligible subject was not reviewed during the inspection.

No prohibited concomitant medications were identified in the patient histories.

At the conclusion of the inspection a one observation, Form FDA- 483 was issued for failure to report to the sponsor adverse effects that may be regarded as caused by the investigational drug. Of the 230 subject records reviewed, the FDA field investigator found that the following were not reported: a) two

instances of hemoglobin change greater than the protocol allowed amount of 3.0 g/dL; and b) five instances of adverse events occurring within 48 hours of procedure. Specifically, Subject 213 had atrial fibrillation, Subject 999 had a small hematoma at the puncture site, Subject 527 had reported back pain, Subject 595 had small oozing at the puncture site, and Subject 793 had agitation.

c. **Assessment of data integrity:** In general, minor record keeping discrepancies were found. Although several instances were found of failure to report adverse events, they are unlikely to significantly impact the primary efficacy outcome of this study. The study was conducted well at this site, and OSI recommends that the data is acceptable in support of the claimed indication.

4. **Clemens Steinwender (formerly Franz Leisch)**
AKH Linz, 1. Med. Abteilung, Krankenhausstrasse 9
Linz, Austria 4020

a. **What was inspected:** This inspection was conducted according to Compliance Program 7348.811. The Clinical Investigator at this site changed after the study had completed from Dr. Franz Leisch who retired in March 2013, to Dr. Clemens Steinwender. Dr. Steinwender signed a Form FDA 1572 on April 4, 2013, to demonstrate his authority in this study. Dr. Steinwender has (b) (4) INDs in CDER's COMIS database, and no prior FDA inspections. At this site, 540 subjects were screened, 539 subjects enrolled, and 530 subjects completed the study. A total of 77 subject files were reviewed to corroborate the data listings with the source documents. For each of these subject files, the FDA field investigator verified the primary efficacy endpoint, and ensured that all adverse events and serious adverse events were appropriately reported.

The inspection included the review of all relevant records, consisting of informed consent documents, protocol and protocol amendments, financial disclosure statements, IRB submissions and correspondence, case report forms, adverse event reporting, clinical source documents, data listings, investigational study medication accountability, monitoring, concomitant medications, and sponsor audit activities.

The FDA field investigator reviewed the informed consent documents for 194 (of 540) subjects to ensure that a signature was obtained prior to the conduct of any study related procedures. He ensured that the protocol was appropriately followed for 18 subject files, and verified that subjects met the inclusion and exclusion criteria, as outlined in the protocol. He reviewed the monitoring records (monitoring was originally done by (b) (4) then switched to (b) (4)) and found that the site adequately followed monitoring recommendations and made corrections, as requested.

b. General observations/commentary: There were no discrepancies found during the corroboration of source documentation and data listings with respect to the primary efficacy endpoint data and adverse events. Although no FDA-483 was issued, the following four items were discussed with staff at the conclusion of the inspection:

1. Four subjects at the beginning of the study were observed not to have a second troponin level taken as required by the protocol, but upon notification by the monitor of this deviation, the site corrected this issue.
2. Five subjects at the beginning of the study were observed not to have their hematology labs taken the morning after the procedures, but upon notification from the monitor, the site corrected this issue.
3. Subject 177 had a screening ECG ordered, but there was no printout of the ECG available in the source records.
4. Subjects 184 and 395 had transcription errors. The source records did not document Plavix was prescribed at discharge, whereas the CRF and the data listings did.

Dr. Steinwender acknowledged these discussion items, and stated that he did not consider that subject safety was jeopardized.

c. **Assessment of data integrity:** Minor protocol deviations were observed. These errors were isolated and unlikely to significantly affect the integrity of the data in support of the indication. No Form FDA 483 was issued. OSI considers that the study was conducted well at this site, and OSI recommends that the data are acceptable in support of the study indication.

5. **Douglas Spriggs**
Clearwater Cardiovascular and Interventional Consultants
455 Pinellas Street, Clearwater, FL 33756

a. **What was inspected:** This inspection was conducted according to Compliance Program 7348.811. Dr. Douglas Spriggs has (b)(4) INDs in COMIS database, and no prior inspection history. At this site, 423 subjects signed the informed consent, 368 subjects entered the study (55 screen failures), and 364 subjects completed the study. The FDA field investigators reviewed informed consent documents (ICD) for 77 subjects and found that all subjects signed ICD before study procedures were begun. The FDA field investigators reviewed data for 77 subjects, selected from the beginning, middle, and end of the study. All subjects listed with a protocol deviation and subjects that experienced a study endpoint were reviewed. The data review consisted of history and physical examinations, laboratory reports, catheter laboratory logs, nurse's notes, and progress reports.

b. General observations/commentary: No discrepancies were found between the sponsor's data listings and the source documents. All adverse events were reported and all endpoint data was verifiable. The field investigators did not find any subjects who experienced IPST, an observation requested by the assignment. Dr. Spriggs also stated that he did not recall any subjects who experienced an IPST.

The majority of subjects with protocol deviations were discontinued from the study and did not receive study medication. One subject (40103098) required a stent placement, and Dr. Spriggs decided the subject would be at high risk for dissection or clot. The intervention was planned for the left main artery so the placement of a stent was cancelled, and the subject did not receive study drug. Two subjects required CABG surgery. One other subject (401030353) was randomized and received study drug before receiving the results of the INR testing. The results were exclusionary. For all subjects enrolled after that time, the FDA field investigators found that INR results were obtained prior to randomization. Drug accountability records were reviewed, and no discrepancies observed.

c. Assessment of data integrity: In general, only very minor discrepancies were found. The study was conducted well at this site, and OSI recommends that the data is acceptable in support of the claimed indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four foreign and one domestic clinical investigator sites were inspected in support of NDA 204958. No regulatory violations were found during the inspections at three foreign sites (Shaburishvili, Khabeishvili, and Steinwender/Leisch) and the domestic site (Spriggs, Florida) . Minor regulatory violations were found during the inspections at Dr.Tousek (Czech Republic), and a one observational Form FDA 483 was issued for failure to report adverse drug reactions. Although regulatory violations were noted as described above, they are unlikely to significantly impact the primary efficacy or safety analysis for this study. Therefore, the data from this study may be considered reliable.

{See appended electronic signature page}

Sharon Gershon, Pharm.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Team Leader and Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

/s/

SHARON K GERSHON
04/29/2014

SUSAN D THOMPSON
04/29/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 20, 2014
Requesting Office or Division:	Division of Cardiovascular & Renal Products (DCRP)
Application Type and Number:	NDA 204958
Product Name and Strength:	Kengreal (cangrelor) for Injection 50 mg per vial
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant:	The Medicines Company
Submission Date:	February 27, 2014 August 30, 2013
OSE RCM #:	2013-1169
DMEPA Primary Reviewer:	Janine Stewart, PharmD
DMEPA Team Leader:	Lisa Khosla, PharmD, MHA

Reference ID: 3474392

1. REASON FOR REVIEW

This review evaluates the proposed labels and labeling for Kengreal (cangrelor) for areas of vulnerability that could lead to medication errors in response to a request from the Division of Cardiovascular & Renal Products (DCRP).

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B- N/A
Previous DMEPA Reviews	C
Human Factors Study	D- N/A
ISMP Newsletters	E- N/A
Other	F- N/A
Container Label, Carton Labeling	G
Full Prescribing Information	H

N/A=not applicable for this review

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed full prescribing information, container label, and carton labeling to identify deficiencies that may lead to medication errors and areas for improvement. We note that the product information, the established name and the strength statement are not presented in the customary fashion , which may cause confusion when trying to locate important product information. We also note that the information regarding the proper storage of the product appears to be inconsistent between the container and carton labeling and the insert labeling. Additionally, we note the use of error prone abbreviations and trailing zeros in dose designations in areas of the full prescribing information. Furthermore, the instructions for preparation and administration of the product can be improved to enhance clarity and decrease confusion. Thus, we provide recommendations to mitigate confusion and promote the safe use of this product in Section 4.

Reference ID: 3474392

4. CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase clarity, readability, and the prominence of important information to promote the safe use of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

Based on this review, we have made revisions to the Full Prescribing Information (See Appendix H) and have provided a detailed summary below for review and consideration by DCRP.

Insert Labeling:

1. The error-prone abbreviation 'IV' can be found in the *Highlights of Prescribing Information* and throughout the *Dosage and Administration* sections. We recommend replacing the abbreviation 'IV' with the appropriate full meaning of 'intravenous'.
2. Trailing zeros is also error-prone and can result in ten-fold error of measurement if the decimal is not seen (i.e. '1.0' can be misinterpreted as '10'); thus, we recommend removing the trailing zeros where they appear in the insert labeling.
3. Revise the statement in Section 2.1 *Recommended Dosing,* [redacted] (b) (4) to the statement "The intravenous bolus dose, followed immediately by the intravenous infusion, should be initiated..." to increase clarity in the dosing information.
4. The Dosage and Administration section instructs the user to dilute the product in normal saline solution at different volumes for PCI [redacted] (b) (4). We recommend incorporating dilution instructions in a table format in a separate section within Section 2, *Dosage and Administration*, that details the preparation and administration similar to the following example:

Reference ID: 3474392

	Preparation			Administration	
Indication	Kengreal®	0.9% Sodium Chloride	Final Concentration	Bolus	Intravenous Rate of Infusion
PCI	50 mg	250 mL	200 µg/mL (0.2mg/mL)	30 µg/kg (over <1 minute)	4 µg/kg/min
[redacted] (b) (4)					

5. Remove storage information statement "[redacted] (b) (4) from Section 2.2. This information is expressed in Section 16.

6. Remove Section 2.3 , [redacted] (b) (4), from the *Dosage and Administration* section. This information is more appropriately expressed in Section 16.

7. Revise Section 16. *How Supplied/ Storage and Handling* to include the product strength and the National Drug Code (NDC). (e.g., Kengreal is supplied in cartons of 10- 10 mL single-use vials containing 50 mg cangrelor as a lyophilized powder for reconstitution. NDC XXXXX-XXX-XX)

4.2 RECOMMENDATIONS FOR THE APPLICANT

DMEPA advises the recommendations below be implemented prior to approval of this NDA.

A. **<u>Container Label</u>:**

1. Revise the order of the product information. The customary order of information should be: proprietary name followed underneath by the full established name, followed underneath by strength; see example below.

   Kengreal
   (cangrelor) for injection
   50 mg per vial

2. Revise the font size of the dosage form to match the font size of the active ingredient because the dosage form is part of the established name and should be consistent.

Reference ID: 3474392

3. Revise the storage condition statement on the side panel to correspond with the storage condition statement in the insert labeling.
4. Add the statement "Must be reconstituted and diluted prior to use" on the principal display panel to highlight these important steps.
5. Remove the [redacted] (b) (4)' statement at the end of the ingredient list. This information is redundant and already presented on the principal display panel .
6. Add the 'Rx Only' statement to the principal display panel per CFR 201.100.
7. Add the usual dosage statement per CFR 201.55 as exhibited in the example below.

   "**Usual Dose:** See package insert for dosage information."

B. **<u>Carton Labeling</u>**:

1. See comments A.1-A.6 above.
2. Ensure the net quantity statement appears in an area of the principal display panel that is away from the product strength and with less prominence to decrease confusion.
3. Move the UPC barcode to the side panel to decrease clutter on the principal display panel.
4. Remove the [redacted] (b) (4) from the principal display panel. This information is customarily provided on the back panel.
5. Revise the reconstitution instructions to read '**Reconstitution:** Add 5 mL of Sterile Water..."
6. Revise the usual dosage statement to read '**Usual Dose:** See package insert for dosing information'.

Reference ID: 3474392

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Kengreal that The Medicines Company submitted on January 16, 2014.

Table 2. Relevant Product Information for Kengreal	
Active Ingredient	Cangrelor
Indication	Reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) [redacted] (b) (4)
Route of Administration	Intravenous
Dosage Form	Lyophilized powder for [redacted] (b) (4)
Strength	50 mg per vial
Dose and Frequency	PCI dose: 30 mcg/kg intravenous (IV) bolus prior to PCI followed immediately by a 4 mcg/kg/min IV infusion for at least 2 hours or duration of procedure whichever is longer. Bridging dose: 0.75 mcg/kg/min infusion continued until surgery. For bridging up to 7 days after discontinuation of oral antiplatelet surgery, patients should receive an intravenous infusion of Kengreal at the rate of 0.75 mcg/kg/min as soon as possible following discontinuation of oral $P2Y_{12}$ inhibition prior to surgery. This infusion can be administered up to 7 days after discontinuation of oral antiplatelet therapy and is maintained until at least 1 hour prior to anesthesia administration for surgery. Each vial must be reconstituted with 5 mL of sterile water for injection, then diluted saline for intravenous infusion.
How Supplied	Sterile lyophilized powder in 10 mL single use glass vials supplied in cartons containing 10 vials
Storage	Store at USP Controlled Room Temperature of [redacted] (b) (4) °C
Container Closure	Glass vial

Reference ID: 3474392

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)- N/A

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the AIMS on February 5, 2014 using the terms, cangrelor, to identify reviews previously performed by DMEPA.

C.2 Results

- **OSE RCM# 2013-1076, dated July 31, 2013**
- **OSE RCM# 2013-1846, dated October 7, 2013**
- **OSE RCM# 2013-2337, dated January 6, 2014**

APPENDIX D. HUMAN FACTORS STUDY- N/A

APPENDIX E. ISMP NEWSLETTERS- N/A

APPENDIX F. OTHER- N/A

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

Reference ID: 3474392

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

/s/

JANINE A STEWART
03/20/2014

LISA V KHOSLA
03/20/2014

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 204958

Application Type: New NDA/NME

Name of Drug: [redacted] (b) (4) (cangrelor) for Injection

Applicant: The Medicines Company

Submission Date: 30 April 2013

Receipt Date: 30 April 2013

1.0 Regulatory History and Applicant's Main Proposals

Please see RPM Filing Review for regulatory history information regarding this submission.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

1. Highlights are greater than one-half page.
2. In the Highlights Limitation Statement, the sponsor included tradename [redacted] (b) (4).
3. Sponsor noted, [redacted] (b) (4) is an [redacted] (b) (4) P2Y12 platelet inhibitor indicated..". Sponsor will be asked to delete, [redacted] (b) (4) [redacted] "
4. All cross-references should be in italics (including the brackets) and there should be no commas between subsection parentheses.
5. In Section 6.1, Clinical Trials Experience, the sponsor did not use the standard CFR statement and did not place it first in the section.

In addition, the following labeling issues were identified:

1. Please remove the trademark symbol (™) after each [redacted] (b) (4) Placing the trademark symbol is appropriate, in either the Highlights title or in the Section 1 after the first mention of the tradename.

Reference ID: 3332982

2. Per 21 CFR 201.57, since there are no studies in the pediatric patient population, subsection 8.4 should read as follows verbatim:

   "Safety and effectiveness in pediatric patients have not been established"

3. Please delete section in the FPI that do not have any content (i.e., Section 15, References).

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by 2August2013. The resubmitted PI will be used for further labeling review.

Reference ID: 3332982

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

NO 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *Sponsor to be instructed in the 74-day letter to reduce the highlights section to a half a page.*

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Reference ID: 3332982

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment: *Sponsor included tradename* (b) (4)

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Reference ID: 3332982

Comment:

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

NO 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Reference ID: 3332982

Comment: *Sponsor noted, [redacted] (b) (4) is an [redacted] (b) (4) P2Y12 platelet inhibitor indicated..". Sponsor will be asked to delete, ' [redacted] (b) (4)*

Dosage Forms and Strengths

YES 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

YES 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

Reference ID: 3332982

Selected Requirements of Prescribing Information (SRPI)

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS

Reference ID: 3332982

Selected Requirements of Prescribing Information (SRPI)

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

N/A 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

NO 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

Reference ID: 3332982

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

NO 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment: *Sponsor did not place the above standard statement first and did not use the CFR language.*

N/A 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

N/A 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

Reference ID: 3332982

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

/s/

ALISON L BLAUS
06/27/2013

OSI/DGCPC CONSULT: Request for Clinical Inspections

Date: 25 June 2013

To: Ann Meeker-O'Connell, Acting Division Director, DGCPC
Constance Lewin, M.D., M.P.H, Branch Chief, GCPEB*
Susan Thompson, M.D., Acting Branch Chief, GCPAB
Janice Pohlman, M.D., M.P.H., Team Leader GCPAB
Susan Leibenhaut, M.D. Acting Team Leader, GCPAB
CDER OSI PM Track
Sharon Gershon
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER

Through: Division of Cardiovascular & Renal Products (DCRP):
Fred Senatore, M.D., Ph.D., Medical Officer
Nhi Beasley, PharmD, Clinical Reviewer
Thomas Marciniak, M.D., CDTL
Norman Stockbridge, M.D., Ph.D., Director

From: Alison Blaus, RAC, Regulatory Health Project Manager, DCRP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 204958
IND#: 56812
Applicant: Medicines Company
ATTN: Steven Sherman, Ph.D.
Senior Director, Global Regulatory Affairs
8 Sylvan Way
Parsippany, NJ 07054
(973) 290-6300
Drug Proprietary Name: [redacted] (b) (4)
Generic Drug Name: cangrelor
NME or Original BLA (Yes/No/Not Applicable*): NME
Review Priority (Standard or Priority or Not Applicable*): Standard
Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No/Not Applicable*): No

**For inspection requests not connected to a PDUFA timeline (i.e., for-cause when marketing application is not pending for product)*

Reference ID: 3331394

Proposed New Indications:

PCI

(b) (4) (cangrelor for injection) is an intravenous (IV) $P2Y_{12}$ platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) [see *Clinical Studies* (14.1)]. In CHAMPION PHOENIX, PLATELEX IV ™ significantly reduced (relative risk reduction [RRR] 22%) the primary composite endpoint of all-cause mortality, myocardial infarction (MI), ischemia driven revascularization (IDR), and stent thrombosis (ST) compared to clopidogrel [see *Clinical Studies* (14.1)].

Bridging

(b) (4) (cangrelor for injection) is indicated to maintain $P2Y_{12}$ inhibition in coronary syndromes (ACS) or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery [see *Clinical Studies* (14.2)].

PDUFA: 29 April 2014
Action Goal Date: 29 April 2014
Inspection Summary Goal Date: 28 February 2014

II. Protocol/Site Identification

All sites noted below are from protocol TMC-CAN-10-01 entitled, "A clinical trial comparing cangrelor to clopidogrel standard of care therapy in subjects who require percutaneous coronary intervention: CHAMPION PHOENIX. Cangrelor versus standard therapy to achieve optimal management of platelet inhibition."

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication/Primary endpoint and other endpoints for verification
#495005 Tamaz Shaburishvili Tbilisi Heart & Vascular Clinic LTD 18/20 Ljubljana Street Tbilisi, Georgia 0159 Email: Tamaz_Shaburishvili@yahoo.com Phone Number: (995) 32 2479300 Fax Number: (995) 32 2479350	TMC-CAN-10-01 CHAMPION - PHOENIX	631	Indication: 1. Reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention. 2. Maintain $P2Y_{12}$ inhibition in acute coronary syndrome patients or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery. Primary End Point: 1. Composite of death, myocardial infarction, ischemia driven revascularization, stent thrombosis 48 hours after randomization. 2. Platelet inhibition >60% at least 80% patient samples. Proportion of patients with PRU<240

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication/Primary endpoint and other endpoints for verification
#495002 George Khabeishvili Diagnostic Services Clinic LTD 36, Ljubljana street Tbilisi, Georgia 0159 Email: georgekhabeishvili@me.com Phone Number: (995) 32 2251000 Fax Number: (995) 32 2251712	TMC-CAN-10-01 CHAMPION - PHOENIX	325	same
#420009 Frantisek Tousek Nemocnice Ceske Budejovice, a.s. Dept Cardiology, B. Nemcove 585/54 Ceske Budejovice, Czech Republic 37087 Email: tousek@nemcb.cz Phone Number: 00420387874301 Fax Number: 00420387874302	TMC-CAN-10-01 CHAMPION - PHOENIX	1063	same
#443002 Franz Leisch AKH Linz 1. Med. Abteilung, Krankenhausstrasse 9 Linz, Austria 4020 Email: franz.leisch@akh.linz.at Phone Number: 004373278060 Fax Number: 4373278066205	TMC-CAN-10-01 CHAMPION - PHOENIX	539	same
#401030 Douglas Spriggs Clearwater Cardiovascular and Interventional Consultants 455 Pinellas Street Suite 400 Clearwater, FL 33756 Email; douglasspriggs@gmail.com Phone Number: 727-445-1911 Fax Number: 727-443-2385	TMC-CAN-10-01 CHAMPION - PHOENIX	368	same

III. Site Selection/Rationale

The primary endpoint is driven by Stent Thrombosis and Type 4a MI. Stent thrombosis itself was driven by intraprocedural stent thrombosis (IPST). The rationale for site selection is to determine:

- **If the sites with the highest enrollment rate drove the primary endpoint.**
- **If IPST was recorded by the Principal Investigator (PI) at the site with the aim of determining potential discrepancies and the frequency of discrepancy between PI angiographic interpretation and adjudication of IPST.**

Domestic Inspections:

Reasons for inspections (please check all that apply):

_X_ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
_X_ Other (specify) **Enrollment of large numbers of study subjects, and significant primary efficacy results.**

Five or More Inspection Sites *(delete this if it does not apply)*:
We have requested these sites for inspection (international and/or domestic) because of the following reasons:

Reasons for site selection

Priority	Site #	Location	# subjects	Reason
1	495005	Tbilisi, Georgia	631	High enrolling site, efficacy endpoints
2	420009	Ceske Budejovice, Czech Republic	1063	highest enrolling site, Eastern Europe site, efficacy endpoints
3	443002	Linz, Austria	539	high enrolling Western Europe site, efficacy endpoints
4	401030	Clearwater, FL USA	368	High enrolling US site without recent inspection; efficacy endpoints
5	495002	Tbilisi, Georgia	325	This site is listed because site 495005 is

				listed. In the trial overall, it is a fairly high enrolling site.

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DGCPC.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact Alison Blaus (Regulatory Project Manager) at 301-796-1138 or Fred Senatore (Medical Officer) at 301-796-1083 or Nhi Beasley (Clinical Reviewer) at 301-796-1504.

Concurrence: (as needed)

_____ Medical Team Leader
_____ Medical Reviewer
_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

******Things to consider in decision to submit request for OSI/DGCPC Audit******

- *Notification by sponsor or applicant that they have identified GCP related concerns at site (such notifications may be submitted to IND or NDA/BLA).*
- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
  - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
  - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Is the concern related to a study conducted under IND?*
- *Were the NDA studies conducted under an IND?*

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

/s/

ALISON L BLAUS
06/25/2013

FORTUNATO F SENATORE
06/26/2013

BACH N BEASLEY
06/26/2013

THOMAS A MARCINIAK
06/27/2013

NORMAN L STOCKBRIDGE
06/27/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 204958 BLA# n/a	NDA Supplement #:S- n/a BLA Supplement # n/a	Efficacy Supplement Type SE- n/a
Proprietary Name: (b) (4) Established/Proper Name: cangrelor Dosage Form: IV Strengths: 30 µg/kg IV bolus followed immediately by 4 µg/kg/min IV infusion		
Applicant: The Medicines Company Agent for Applicant (if applicable): n/a		
Date of Application: 30 April 2013 Date of Receipt: 30 April 2013 Date clock started after UN: n/a		
PDUFA Goal Date: 30 April 2014	Action Goal Date (if different): n/a	
Filing Date: 29 June 2013	Date of Filing Meeting: 4 June 2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1 - NME		
Proposed indication(s)/Proposed change(s): PCI and Bridging.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	

Reference ID: 3323200

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*): n/a

List referenced IND Number(s): 56812

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified: n/a				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

Reference ID: 3323200

User Fee Status	Payment for this application:
If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**			X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***			X	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:			X	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***		X		

Reference ID: 3323200

Designations and Approvals list at: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*				
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			x	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: FIVE ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	x			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		x		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			x	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	x			
Index: Does the submission contain an accurate comprehensive index?	x			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	x			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

Reference ID: 3323200

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			x	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	x			
Are all establishments and their registration numbers listed on the form/attached to the form?	x			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	x			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	x			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	x			

Reference ID: 3323200

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	x			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***		x		This is an electronic NDA.
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:			x	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be*	x			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

Reference ID: 3323200

reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***		X		A REMS was not requested at the pre-NDA.
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL	X			

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

Reference ID: 3323200

format? ***If no, request applicant to submit SPL before the filing date.***				
Is the PI submitted in PLR format?[4]	X			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			X	No MedGuide or PPI submitted
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	X			OSI have been consulted

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

Reference ID: 3323200

If yes, specify consult(s) and date(s) sent:				
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 6 July 2005 ***If yes, distribute minutes before filing meeting***	X			Minutes dated 4Aug05 (CHAMPION)
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** BRIDGE Topline on 14May12, Follow-up Topline on 15Aug12 & pre-NDA on 20Nov12; PHOENIX Topline on 25Feb13 ***If yes, distribute minutes before filing meeting***	X			Minutes dated: BRIDGE Topline 8Jun12, BRIDGE pre-NDA 26Dec12, BRIDGE Follow-up Topline 12Sep12; PHOENIX Topline 3Apr13
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

Reference ID: 3323200

ATTACHMENT

MEMO OF FILING MEETING

DATE: 4 June 2013

NDA #: 204958

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: cangrelor

DOSAGE FORM/STRENGTH: 30 µg/kg IV bolus followed immediately by 4 µg/kg/min IV infusion

APPLICANT: The Medicines Company

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

PCI

(b) (4) (cangrelor for injection) is an intravenous (IV) $P2Y_{12}$ platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) [see *Clinical Studies* (14.1)].

In CHAMPION PHOENIX, PLATELEX IV™ significantly reduced (relative risk reduction [RRR] 22%) the primary composite endpoint of all-cause mortality, myocardial infarction (MI), ischemia driven revascularization (IDR), and stent thrombosis (ST) compared to clopidogrel [see *Clinical Studies* (14.1)].

Bridging

(b) (4) (cangrelor for injection) is indicated to maintain $P2Y_{12}$ inhibition in patients with acute coronary syndromes (ACS) or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery [see *Clinical Studies* (14.2)].

BACKGROUND:

Cangrelor is a reversible, short-acting, parenteral inhibitor of platelet P2Y12 receptors. The Medicines Company (TMC) developed cangrelor for (b) (4)

Reference ID: 3323200

The Medicines Company has completed the following clinical studies:

Phase 2

- ***BRIDGE*** – A randomized, double-blind, placebo-controlled study comparing administration of cangrelor to placebo in patients who had discontinued clopidogrel prior to coronary artery bypass grafting (CABG), attempting to maintain platelet inhibition until shortly before CABG. The primary efficacy endpoint was the proportion of subjects with P2Y12 Reaction Units (PRU) < 240 measured by the VerifyNow P2Y12 Test device during the entire period prior to CABG. The trial demonstrated that intravenous cangrelor at a dose of 0.75 µg/kg/min for several days consistently maintained platelet P2Y12 inhibition at PRU < 240.

Phase 3

- ***CHAMPION STUDIES*** - The primary endpoint in both studies was the composite of all-cause mortality, myocardial infarction, and ischemia-driven revascularization. Enrollment in both studies was terminated following an interim analysis indicating there was low likelihood of achieving the primary endpoint.
  - ***CHAMPION PCI*** - A randomized, double-blind, double-dummy, active-controlled, parallel group clinical trial in patients who required PCI, including patients with STEMI. Patients randomized to the cangrelor group received cangrelor (30 µg/kg bolus followed immediately by 4 µg/kg/min infusion) for at least 2 hours or for the duration of the PCI procedure, whichever was longer, followed by 600 mg clopidogrel after the end of the infusion. Patients randomized to the clopidogrel group received a 600 mg loading dose of clopidogrel before the start of the PCI procedure.
  - ***CHAMPION PLATFORM*** - A randomized, double-blind, placebo-controlled, parallel group trial in patients with stable/unstable angina or NSTEMI who required PCI. Patients were randomized to receive either placebo or cangrelor (30 µg/kg bolus followed immediately by 4 µg/kg/min infusion) prior to the procedure. Unlike Champion-PCI, patients in the control group did not receive a dose of clopidogrel at the start of the PCI procedure; instead, clopidogrel was given at the end of the PCI procedure to both groups.
- ***PHOENIX*** - A randomized, double-blind, parallel group, superiority study comparing cangrelor to clopidogrel in subjects who require PCI. The primary objective was to demonstrate that cangrelor reduces the risk of a composite of all-cause mortality, myocardial infarction, ischemia driven revascularization, and stent thrombosis compared to clopidogrel.

We have met with the sponsor on a number of occasions regarding the three trials submitted, CHAMPION (PCI & PLATFORM), BRIDGE, and PHOENIX. The last meeting was on 25Feb13 (minutes dated 3Apr13), regarding the PCI indication (PHOENIX), discussed the topline results from the trial. A pre-NDA meeting was held on 20Nov12 (minutes dated 26Dec12) discussing the results from the BRIDGE trial (second proposed indication). TMC is requesting a priority review.

Reference ID: 3323200

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Alison Blaus	Y
	CPMS/TL:	Edward Fromm	Y
Cross-Discipline Team Leader (CDTL)	Tom Marciniak		N
Clinical	Reviewer:	Fred Senatore (efficacy) Nhi Beasley (safety)	Y Y
	TL:	n/a	n/a
Social Scientist Review (*for OTC products*)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
OTC Labeling Review (*for OTC products*)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Steven Donald	Y
	TL:	n/a	n/a
Clinical Pharmacology	Reviewer:	Sreedharan Sabarinath	Y
	TL:	Raj Madabushi	Y
Biostatistics	Reviewer:	Jialu Zhang	Y
	TL:	Jim Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Belay Tesfamarian	Y
	TL:	Al DeFelice	N
Statistics (carcinogenicity)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Product Quality (CMC)	Reviewer:	David Claffey	Y

Reference ID: 3323200

	TL:	Kasturi Srinivasachar	Y
Quality Microbiology *(for sterile products)*	Reviewer:	Steven Donald	Y
	TL:	n/a	n/a
CMC Labeling Review	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Facility Review/Inspection	Reviewer:	n/a	n/a
	TL:	n/a	n/a
OSE/DMEPA (proprietary name)	Reviewer:	Kim DeFronzo	Y
	TL:	Irene Chan	Y
OSE/DRISK (REMS)	Reviewer:	Somya Dunn	Y
	TL:	n/a	n/a
OC/OSI/DSC/PMSB (REMS)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Bioresearch Monitoring (OSI)	Reviewer:	Sharon Gershon	Y
	TL:	Susan Leibenhaut	N
Controlled Substance Staff (CSS)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Other reviewers	Margie Goulding (OSE-EPI)		Y
Other attendees	Norman Stockbridge (Division Director), Steve Grant (Deputy Director)		

FILING MEETING DISCUSSION:

GENERAL	
• 505(b)(2) filing issues:	☒ Not Applicable
○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☐ NO
○ Did the applicant provide a scientific	☐ YES ☐ NO

Reference ID: 3323200

"bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: No Comments	☐ Not Applicable
CLINICAL **Comments**: The bookmarks were not easily discernible, but this is not a filing issue. RPM will check with reviewers closer to the 74day date regarding review issues for the letter.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☒ YES Date if known: one day between 12-14 January 2014 ☐ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

Reference ID: 3323200

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**: No issues at this time for the 74day letter	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: No issues at this time for the 74day letter	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**: No issues at this time for the 74day letter	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Reference ID: 3323200

Comments: No issues at this time for the 74day letter	☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☒ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**: One issue for the 74day letter	☐ Not Applicable ☒ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

Reference ID: 3323200

APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)	☐ N/A
• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?	☐ YES ☒ NO
• If so, were the late submission components all submitted within 30 days?	☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	n/a
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Robert Temple, M.D. **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): 7October2013 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	

Reference ID: 3323200

REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Reference ID: 3323200

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

Reference ID: 3323200

(3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Reference ID: 3323200

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

/s/

ALISON L BLAUS
06/11/2013