

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204958Orig1s000

CHEMISTRY REVIEW(S)

NDA 204958
Resubmission

Cangrelor
Powder For [REDACTED]^{(b) (4)}, Lyophilized

The Medicines Company

Office of Pharmaceutical Quality
for
Division of Cardiology and Renal Products

Wendy I. Wilson-Lee, Ph.D. – Application Technical Lead
Okpo Eradiri, Ph.D. – Biopharmaceutics Reviewer
Michael Shanks – Facilities Reviewer

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Chemistry Review Data Sheet

1. NDA: 204958
2. REVIEW: #2
3. REVIEW DATE: 15-JUN-2015
4. REVIEWER: Wendy I. Wilson-Lee; Okpo Eradiri; Michael Shanks
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Memorandum to File – Overall CMC Recommendation	15-APR-2014
CMC Review #1	12-DEC-2013

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Resubmission	23-DEC-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	The Medicines Company
Address:	8 Sylvan Way Parsippany, NJ 07054
Representative:	Andrew F. Friedman, PharmD VP, Regulatory Affairs
Telephone:	973-290-6027

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	(b) (4)
b) Non-Proprietary Name (USAN):	Cangrelor tetrasodium
c) Code Name/# (ONDQA only):	(b) (4); AR-C69931MX
d) Chem. Type/Submission Priority (ONDQA only):	
• Chem. Type:	1
• Submission Priority:	S

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

10. PHARMACOL. CATEGORY: Antiplatelet

11. DOSAGE FORM: Powder For (b) (4), Lyophilized

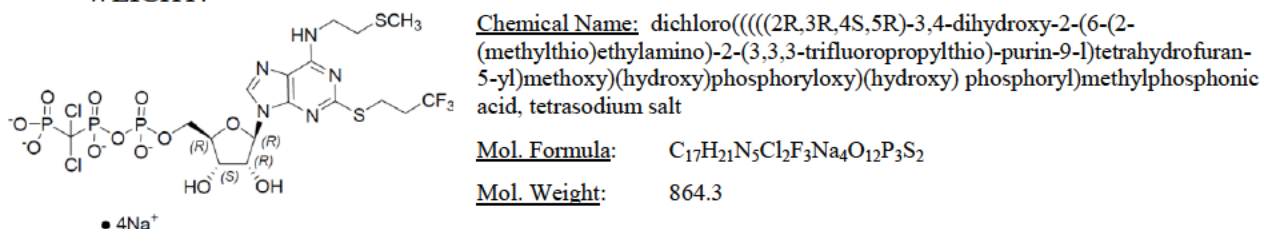
12. STRENGTH/POTENCY: 50 mg

13. ROUTE OF ADMINISTRATION: Intravenous

Executive Summary Section

14. Rx/OTC DISPENSED: X Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed X Not a SPOTS product

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



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF # (b) (4)	TYPE	HOLDER	ITEM REFERENCED (b) (4)	CODE ¹	STATUS ²	REVIEW DATE	COMMENTS
	III			7	Adequate	12-DEC-2013	No changes, acceptable first cycle
	II			7	Adequate	12-DEC-2013	See above
	III			7	Adequate	12-DEC-2013	See above

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	56812	Cangrelor for injection for percutaneous transluminal coronary angioplasty with or w/o intracoronary stent placement
NDA	22433	For BE study for over-encapsulated clopidogrel used as comparator

18. STATUS:

CONSULTS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	-	-
EES	Approval	14-JUN-2015	M. Shanks
Pharm/Tox	N/A	-	-
Biopharm	Acceptable		O. Eradiri
LNC	N/A	-	-
Methods Validation	Acceptable	07-NOV-2013	M. Trehy
DMEPA	N/A	-	-
EA	Categorical exclusion granted	12-DEC-2013	D. Claffey
Microbiology	Approvable pending labeling of in-use conditions	06-JAN-2014	S. Donald

Chemistry Review for NDA 204958

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

We recommend approval, from a product quality perspective, of Cangrelor Powder for (b) (4), Lyophilized when stored in 10 mL USP (b) (4) glass vials sealed with (b) (4) grey (b) (4) stoppers and capped with flip-off aluminum overseals.

We grant a 24 month drug product shelf-life when stored at controlled room temperature in the intended commercial packaging configuration. We grant a 24 hour in-use period for the drug product solution when reconstituted with 5 mL of Sterile Water for Injection and diluted with 0.9% Sodium Chloride Injection and stored at room temperature. We grant a 12 hour in-use period for the drug product solution when reconstituted with 5 mL of Sterile Water for Injection and diluted with 5% Dextrose Injection and stored at room temperature.

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

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug substance: The drug substance is a water-soluble white amorphous tetrasodium salt. It is an ATP analogue with a dichloromethylene group between the second and third phosphate and two different thioethyl groups on the base. It is designed as a P2Y12 platelet receptor antagonist to block ADP-induced platelet activation and aggregation. It is stated to provide fast-onset, potent, and consistent P2Y12 inhibition, with reversible binding and a half-life of 3 to 6 minutes. The proposed indications are for the reduction of thrombotic events (including stent thrombosis) in patients with coronary artery disease undergoing PCI and for maintaining P2Y12 inhibition in ACS patients or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral P2Y12 therapy is interrupted due to surgery. Details of its manufacture and control are cross referenced to DMF (b) (4). This was found adequate to support this application (David Claffey, 10 DEC 2013). Manufacturing involves several synthetic steps. Two genotoxic impurities are controlled at intermediate (b) (4) and the bulk of the remaining impurities and residual reagents and solvents are controlled at drug substance release. The drug substance release specification was adequately justified in DMF (b) (4). The drug substance is stored at (b) (4). Data were provided to support the proposed retest date.

Drug product: The drug product will be supplied as a sterile lyophilized (b) (4) in single-use glass vial. Each vial is designed to deliver 50 mg of cangrelor (based on free acid) in 10 ml (b) (4) clear glass vials fitted with grey 20 mm (b) (4) rubber stopper and sealed with 20 mm aluminum 'flip-off' overseal. The vial contains a target (b) (4) mg of cangrelor tetrasodium (this amount includes both the sodium ion and a (b) (4) overage). Cangrelor is intended for intravenous administration after reconstitution with 5ml sterile water for injection. The only excipients are mannitol and sorbitol. The proposed commercial formulation

Executive Summary Section

and single 50 mg strength was used for all the Phase III studies. The clinical product was manufactured at two sites, (b) (4) from lots of drug substance manufactured at (b) (4). The commercial product will be manufactured at (b) (4). The manufacturing process is typical for a lyophilized IV-administered product. The lyophilization process was designed to product a (b) (4) which is can be stored at room temperature.

Studies to demonstrate the compatibility of cangrelor with the infusion solutions were found to be adequate after additional studies were conducted at Agency request. The in-use expiry periods are limited by the results of microbial stability studies which support a 12 hour expiry period in D5W and 24 hours in saline. Drug interaction studies found cangrelor formed a precipitate with 18 out of 101 drug solutions tested. These incompatible drugs are listed in the proposed label.

The drug product specification is typical for an intravenously administered product. Data were provided from eight registration lots – three from (b) (4), three from (b) (4) and two from the (b) (4), the proposed commercial site. Data up to 48 months were provided for the non-commercial sites and results through 24 months were provided for the commercial site. Accelerated data through six months were provided for each of the eight batches. All results remained within specified limits with no trends apparent apart from the (b) (4) and content of specified degradants (b) (4) and (b) (4). Few differences were apparent between batches or manufacturing sites – except for the slower reconstitution time from the lots originating from the (b) (4) site. The proposed 24 months drug product expiration is supported by real time data from two batches manufactured at the commercial site (one pilot scale, one commercial scale) as well as six batches from non-commercial manufacturing sites.

B. Description of How the Drug Product is Intended to be Used

The drug product is intended for IV administration over two hours or for the duration of the surgical procedure, whichever is longer, up to four hours. The drug product should be reconstituted with 5 mL of Sterile Water for Injection and further diluted with either 5% Dextrose Injection or 0.9% Sodium Chloride Injection in IV bags prior to use. The reconstituted solution is stable for up to 24 hours at room temperature. The diluted solution is stable for up to 12 hours in 5% Dextrose Injection and up to 24 hours in 0.96% Sodium Chloride Injection. Any remaining solution in the bag and vial should be discarded after 24 hours.

C. Basis for Approvability or Not-Approval Recommendation

We recommend approval from a product quality perspective. The resubmission contained updated CMC information regarding drug product stability (long-term and in-use), drug product specification (revised acceptance criterion for (b) (4) specified degradant, bioequivalence data to support the use of over-encapsulated clopidogrel as the comparator in the pivotal clinical study, and a revised drug product shelf-life (24 months). All new CMC information provided in the resubmission was reviewed and found acceptable to support marketing of the drug product under NDA 204958. The drug product, biopharmaceutics, and facility reviewers all recommend approval. Therefore, the overall OPQ quality recommendation is approval.

III. Administrative

A. Reviewer's Signature



Chemistry Assessment

Summary of Biopharmaceutics Review

The Division of Pharmaceutics issued a CR comment regarding the “lack of documentation on bioequivalence of the over-encapsulated clopidogrel clinical supplies to the US approved clopidogrel product. The over-encapsulated clopidogrel served as the comparator during the pivotal clinical trials supporting approval of cangrelor. The applicant responded to the biopharmaceutics CR comment in the resubmission, providing right of reference to Astra-Zeneca’s BE study comparing over-encapsulated and non-capsulated clopidogrel tablets (NDA 22433) and comparative dissolution data at pH 2.0, 4.5, and 6.8 for the over-encapsulated and non-capsulated clopidogrel tablets. The biopharm team found that the applicant adequately addressed the CR comment. **The Biopharmaceutics recommendation is approval.** Refer to the Biopharmaceutics Quality Assessment review (Okpo Eradiri, 26-MAY-2015) in Panorama.

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3:

S DRUG SUBSTANCE [Cangrelor, (b) (4)]

No new drug substance information was provided in the NDA or in the referenced DMF.

P DRUG PRODUCT [(b) (4) (cangrelor); Powder, For (b) (4), Lyophilized]

The resubmission includes an update to the following CMC information:

- Additional long-term stability data (24 months) from the registration stability studies manufactured at the proposed commercial manufacturing site (b) (4)
- Revised compatibility information highlighting an observed increase in the content of specified degradants (b) (4) under in-use conditions
- Revised acceptance criterion for specified degradant (b) (4) in the drug product specification
- (b) (4) in the proposed drug product shelf-life to 24 months instead of the original (b) (4) month proposal based on the additional stability data

Specification (copied from submission)

NDA 204958

Cangrelor Powder For (b) (4) Lyophilized

Table 1: Cangrelor for Injection Specifications for Release and Shelf-Life

Test	Acceptance Criteria	Method
Description	White to off white lyophilized solid	Visual
Description of Constituted Solution	Clear, colorless to pale yellow solution essentially free from particulate matter	Visual
Reconstitution Time	(b) (4) seconds	Visual
pH	(b) (4) After reconstitution with 5ml Water	USP <791> Ph Eur 2.2.3
(b) (4)		
Identification by HPLC ^a	Conform	HPLC
Identification by UV ^a	Conform	HPLC
Assay of Cangrelor	(b) (4)% of the theoretical content (b) (4) mg	HPLC
Content Uniformity ^a	Meet USP <905> and Ph.Eur 2.9.40 requirements	HPLC
Particulate Matter ^b	≥ (b) (4) μm NMT (b) (4) particles/vial ≥ (b) (4) μm NMT (b) (4) particles/vial	USP <788> Ph.Eur 2.9.19
Degradation products (b) (4)	≤ (b) (4) % ≤ (b) (4) % ≤ (b) (4) % ≤ (b) (4) % ≤ (b) (4) % Unspecified	HPLC
Total Degradants	Release ≤ (b) (4) % Shelf-life ≤ (b) (4) %	
Bacterial Endotoxin ^b	≤ (b) (4) U/mg	USP <85> Ph.Eur 2.6.14
Sterility ^b	Sterile	USP <71> Ph.Eur 2.6.1

^a For release testing only

^b Tests to be conducted annually for shelf-life

Evaluation: Adequate – The original submission included a proposed (b) (4) acceptance criterion of ≤ (b) (4)%. Based on the (b) (4) in (b) (4) content observed, the applicant proposes (b) (4) acceptance criterion of ≤ (b) (4)%. Based on the maximum daily dose of 50 mg, the revised acceptance criterion of ≤ (b) (4)% for specified degradant (b) (4) is acceptable based on the ICH Q3B qualification limit (≤ 0.5%).

The specification includes different acceptance criterion for total degradants at release (≤ (b) (4)%) and shelf-life (≤ (b) (4)%). During the first review cycle, we requested that the applicant revise this attribute to include one limit based on shelf-life with the proposed release limit used as an internal control strategy. The applicant requested that the dual criteria remain to allow for a harmonized specification with other global territories that require additional regulatory control at release. We accepted the applicant’s justification during the first review cycle. No changes to align the total degradants criteria will be requested.

Compatibility

The applicant revised Section 3.2.P.2.6 Compatibility to indicate that changes in the content of the degradation products (b) (4) were observed during the in-use period. The original submission, as amended, only identified (b) (4) content during the in-use period. Despite the observed (b) (4), the content of both degradants complied with the proposed acceptance criterion for each. Based on these results, the applicant revised the overall recommendation, indicating that the diluted solution is stable for at least 24 hours in-use in contrast to the (b) (4) hours as noted in the original submission.

Evaluation: Adequate – The first cycle review noted that the content of (b) (4) exceeded the specified limit after (b) (4) hours in saline injection and that the content of (b) (4) approached the specified limit after (b) (4) hours in dextrose injection. Due to concerns regarding the microbial quality of the solution diluted with dextrose injection, a 12 hour in-use period was recommended for the dextrose dilution. The compatibility

NDA 204958 Cangrelor Powder For (b) (4), Lyophilized data was determined to support a 24 hour in-use expiry when diluted with saline injection. Based on the data provided in the resubmission and the chemical and microbiological quality assessments of the proposed in-use periods from the first cycle review, **we grant a 24 hour in-use period for the drug product solution when reconstituted with 5 mL of Sterile Water for Injection and diluted with 0.9% Sodium Chloride Injection and stored at room temperature. We grant a 12 hour in-use period for the drug product solution when reconstituted with 5 mL of Sterile Water for Injection and diluted with 5% Dextrose Injection and stored at room temperature.**

Stability Summary

Long-Term Stability Data

The original submission included data through six months at long-term conditions for the two batches manufactured at the commercial drug product manufacturing site ((b) (4); Batch TT248, (b) (4) scale; Batch 00001, (b) (4) scale) and data through 24 months at long-term conditions for one batch manufactured at the registration stability site ((b) (4), Batch 2070017, (b) (4) scale). The resubmission included data through 24 months at long-term conditions for the commercial drug product site batches ((b) (4) Batches TT248 and 00001) and through 36 months for the registration stability batch ((b) (4) Batch 2070017).

(b) (4) **Batch:** All results complied with the acceptance criteria. A slight increase in (b) (4) was observed at Month 36 ((b) (4)%) compared to Month 24 ((b) (4)%).

(b) (4) **Batches:** All results complied with the acceptance criteria. A slight decrease in reconstitution time was observed for both batches.

In-Use Stability Data

The applicant revised the proposed drug product shelf-life from (b) (4) months to 24 months based on the available long-term and in-use stability data. Although the long-term stability data supports the original (b) (4) month shelf-life proposal, the applicant found that batches containing the highest observed contents of the (b) (4) degradants resulted in (b) (4) degradant contents that approached the specification limits for each degradant during the (b) (4). Based on these results, the applicant (b) (4), 24 months for the batches manufactured at the intended commercial site. The original review noted that due to microbial in-use stability concerns, the in-use period for the reconstituted solution diluted with 5% Dextrose Injection is capped at 12 hours.

Evaluation: Adequate – The updated stability data support the use of the drug product through the proposed shelf-life when stored at controlled room temperature. However, the applicant revised the proposed drug product shelf-life based on results from the in-use stability study. Based on the data provided and in accordance with ICH Q1E, **we grant a 24 month drug product shelf-life when stored at controlled room temperature in the intended commercial packaging configuration.**

A APPENDICES

A.1 Facilities and Equipment (biotech only)

NDA 204958

Cangrelor Powder For (b) (4), Lyophilized

Not applicable

A.2 Adventitious Agents Safety Evaluation

Not applicable

A.3 Excipients

Not applicable

R REGIONAL INFORMATION**R1 Executed Batch Records**

The original submission included executed batch records.

R2 Comparability Protocols

None

R3 Methods Validation Package

Methods validation by FDA Labs was acceptable during the first review cycle. The resubmission does not include changes to the proposed regulatory analytical procedures.

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1**A. Labeling**

The applicant incorporated all recommended changes from a product quality perspective in the prescribing information during the first cycle.

Evaluation: Adequate – The new proposed proprietary name is (b) (4). The information regarding storage and in-use period was incorporated into the label during the first review cycle. **The carton, container, and PI are acceptable from a product quality perspective.**

B. Environmental Assessment Or Claim Of Categorical Exclusion

The original submission included a claim for categorical exclusion in accordance with 21 CFR 25.31 based on an expected introduction concentration of < 1 ppb. In addition, in accordance with 21 CFR 25.15(d), the applicant indicated that no extraordinary circumstances exist.

Evaluation: Adequate – The claim for categorical exclusion is granted.

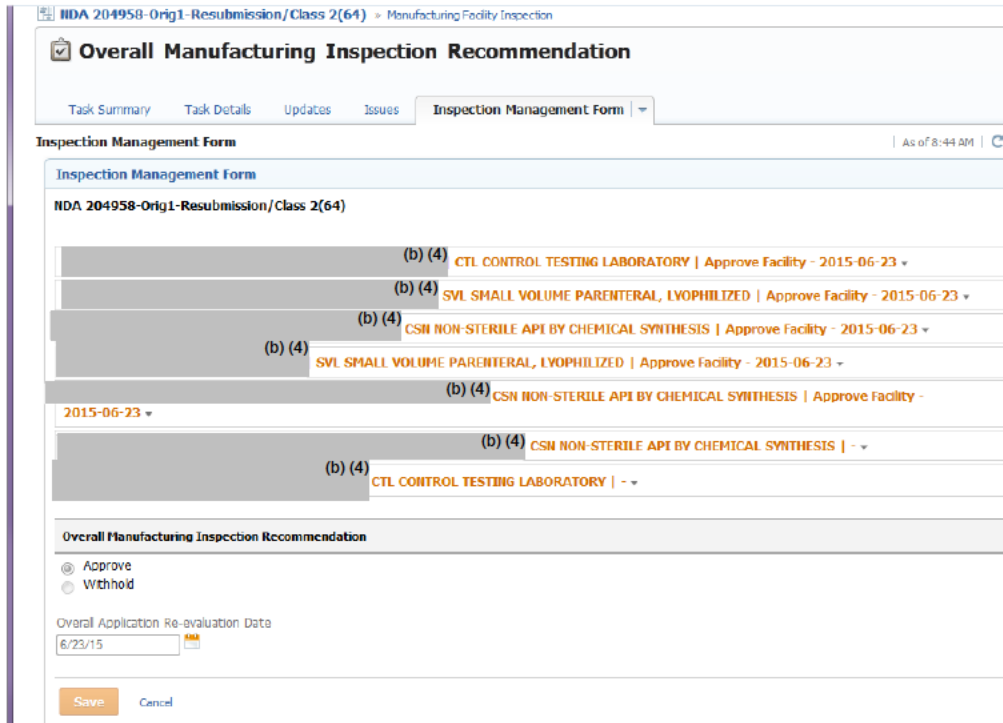
C. Establishment Inspection

NDA 204958

Cangrelor Powder For (b) (4), Lyophilized

The Division of Inspectional Assessment in the Office of Process and Facilities evaluated five facilities and found all to be acceptable from a cGMP perspective. Two facilities submitted as part of the original submission were withdrawn from the resubmission on 04/14/2014 in Quality Response Sequence 0058 (59) – (b) (4) and (b) (4)

Although these facilities appear in the Panorama Inspection Report, these facilities no longer support NDA 204958 and do not impact the overall compliance recommendation. **The overall compliance recommendation is approval.** Refer to the Facility Primary Quality Assessment (Michael Shanks, 14-JUN-2015) and Panorama Inspection Report.



NDA 204958-Orig1-Resubmission/Class 2(64) > Manufacturing Facility Inspection

Overall Manufacturing Inspection Recommendation

Task Summary Task Details Updates Issues Inspection Management Form

Inspection Management Form | As of 8:44 AM

Inspection Management Form

NDA 204958-Orig1-Resubmission/Class 2(64)

- (b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility - 2015-06-23
- (b) (4) SVL SMALL VOLUME PARENTERAL, LYOPHILIZED | Approve Facility - 2015-06-23
- (b) (4) CSN NON-STERILE API BY CHEMICAL SYNTHESIS | Approve Facility - 2015-06-23
- (b) (4) SVL SMALL VOLUME PARENTERAL, LYOPHILIZED | Approve Facility - 2015-06-23
- (b) (4) CSN NON-STERILE API BY CHEMICAL SYNTHESIS | Approve Facility - 2015-06-23

Overall Manufacturing Inspection Recommendation

Approve
 Withhold

Overall Application Re-evaluation Date
6/23/15

Save Cancel

III. List Of Deficiencies To Be Communicated

None

Kengreal (cangrelor) for Injection

NDA 204958

Summary Basis for Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: The Medicines Company
8 Sylvan Way
Parsippany, NJ 07054

Proposed Indication: Reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI); to maintain P2Y₁₂ 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 P2Y₁₂ inhibitor therapy is interrupted due to surgery.

Presentation: The product is supplied as a 50 mg sterile lyophilized powder in a single use, 10 ml glass vial.

EER Status: Overall recommendation is “Acceptable” as of 15-Apr-2014

Consults: ONDQA Biopharmaceutics – Review not needed.

Microbiology- Acceptable with labeling change for in-use period (Steven P. Donald, 6-Jan-2014)

Methods Validation – Acceptable (7-Nov-2013, Michael L. Trehy)

EA – Categorical exclusion granted.

Post-Approval Agreements: None

Drug Substance:

The drug substance, cangrelor tetrasodium, is a new molecular entity. It is a white to off-white, amorphous solid which contains four chiral centers. The drug substance is synthesized by a third party vendor and information is provided in a Drug Master File (DMF). The DMF was found to be “adequate” to support this application. The synthesis involves a multistep process.

The drug substance quality is ensured through in-process controls throughout the manufacturing process and the appropriate final drug substance specification. The drug substance acceptance specification includes tests and acceptance criteria for drug substance critical quality attributes, e.g., physical description, identification, counter ion assay, assay, specific rotation, impurities, residual solvents, heavy metals, microbial limits, water contents and endotoxin limits. The analytical procedures have been adequately described and validated to control the quality of the drug substance. The stability of the drug substance has been demonstrated through appropriate stability studies to support an assigned (b) (4) month retest period for the drug substance when stored at (b) (4).

Drug product:

Kengreal (cangrelor) for injection is a lyophilized product which is supplied in a single use glass vial. Each vial contains (b) (4) mg of cangrelor tetrasodium salt which will deliver 50 mg of free acid after reconstitution. The product is intended for intravenous administration after reconstitution with WFI. The drug product formulation contains mannitol and sorbitol as excipients. The manufacturing process includes (b) (4). The manufacturing process has appropriate in-process controls to ensure the quality of the drug product. The product quality is further ensured through end product testing. The end product specification includes testing for description, identification, assay, content uniformity, reconstitution time, degradation products, sterility, and endotoxin contents. All analytical procedures for the drug product are adequately described and validated. The provided stability data support the proposed (b) (4) month expiration period for this product. The in-use shelf-life of the diluted solution after initial reconstitution is limited to 12-hours in D5W and 24-hours in saline.

The drug product is stored at (b) (4) with excursions permitted 15-30°C (59-86°F).

Conclusion: Adequate from CMC perspective.

Additional Items:

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Overall Conclusion: The application is recommended for “**Approval**” from CMC perspective. The Microbiology reviewer has recommended that the in-use period for D5W diluted product [REDACTED] ^{(b) (4)} 12 hours in the labeling during labeling negotiations.

Ramesh K. Sood, Ph.D.
Acting Director, DPA I/ONDQA

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(CCI/TS) immediately following this page

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

/s/

RAMESH K SOOD
04/16/2014

MEMORANDUM

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

DATE: 15 APR 2014
FROM: David J. Claffey, Ph.D., ONDQA
RE: NDA 204958
SUBJECT: **Approval Recommendation from a CMC perspective**

CMC Review #1 recommended approval on receipt of an overall acceptable recommendation from CDER Office of Compliance (OC). The 14 APR 2014 amendment provided the requested updated 356(h) form which removed the shuttered (b)(4) site from the application and clarified the responsibilities of the (b)(4) site as being a clinical rather than a commercial drug product manufacturer. CDER OC issued an overall acceptable recommendation on 15 APR 2014. **Therefore an overall approval recommendation can now be made from a CMC perspective.**

Note that although the (b)(4) site manufactured three registration stability batches, the data from batches manufactured at the (b)(4) sites support the proposed (b)(4) month expiry period.

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

/s/

DAVID J CLAFFEY
04/15/2014

NDA 204958

Cangrelor for Injection

The Medicines Company

David J. Claffey, PhD

ONDQA

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Chemistry Review Data Sheet

1. NDA 204958
2. REVIEW #:1
3. REVIEW DATE: 12 DEC 2013
4. REVIEWER: David J Claffey, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Initial

30 APR 2013

Amendment N-0025 Response to IR

25 OCT 2013

Amendment N-0027 Response to IR

8 NOV 2013

Amendment N-0029 Response to IR

15 NOV 2013

Amendment N-0032 Response to IR

5 DEC 2013

7. NAME & ADDRESS OF APPLICANT:

Name:

The Medicines Company

Address:

Parsippany, NJ

Representative:

Stephen Sharman

Chemistry Review Data Sheet

Telephone:

973-290-6300

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: (b) (4)
- b) Non-Proprietary Name (USAN): Cangrelor tetrasodium
- c) Code Name/# (ONDC only): (b) (4) AR-C69931MX
- d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Platelet inhibitor

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 50 mg

13. ROUTE OF ADMINISTRATION: IV infusion

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#) SPOTS product – Form Completed Not a SPOTS product

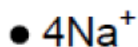
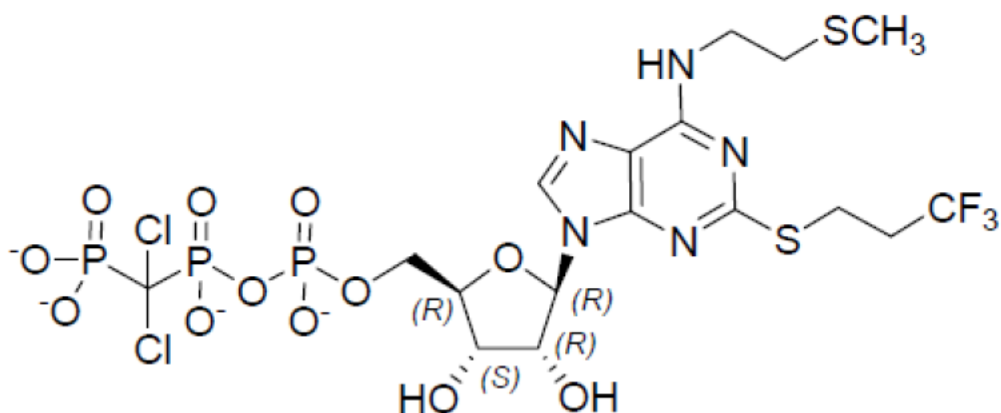
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

dichloro((((2R,3R,4S,5R)-3,4-dihydroxy-2-(6-(2-(methylthio)ethylamino)-2-(3,3,3-trifluoropropylthio)-purin-9-yl)tetrahydrofuran-5-yl)methoxy)(hydroxy)

Chemistry Review Data Sheet

phosphoryloxy)(hydroxy)phosphoryl)methylphosphonic acid, tetrasodium salt

N₆-[2-[(methylthio)ethyl]-2-[(3,3,3-trifluoropropyl)thio]-5'-adenylic acid, monoanhydride with (dichloromethylene)bis[phosphonic acid], tetrasodium salt



C₁₇H₂₁N₅Cl₂F₃Na₄O₁₂P₃S₂

864.3 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	I	(b) (4)	(b) (4)	3	Adequate	24 JUL 2008	
	II			1	Adequate	12 DEC 2013	
	I			3	Adequate	30 NOV 2005	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

Chemistry Review Data Sheet

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Pending		
EES	Pending		
Pharm/Tox	Pending		
Biopharm	Review not needed	11 JUN 2013	Kareen Riviere
Methods Validation	Acceptable	7 NOV 2013	Michael L Trehy
EA	N/A		
Microbiology	Pending		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

The Chemistry Review for NDA 204958

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend approval from CMC perspective on receipt of an overall acceptable recommendation from CDER Office of Compliance.

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

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug substance: The drug substance is a water-soluble white amorphous tetrasodium salt. It is an ATP analogue with a dichloromethylene group between the second and third phosphate and two different thioethyl groups on the base. It is designed as a P2Y₁₂ platelet receptor antagonist to block ADP-induced platelet activation and aggregation. It is stated to provide fast-onset, potent, and consistent P2Y₁₂ inhibition, with reversible binding and a half-life of 3 to 6 minutes. The proposed indications are for the reduction of thrombotic events (including stent thrombosis) in patients with coronary artery disease undergoing PCI and for maintaining P2Y₁₂ inhibition in ACS patients or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral P2Y₁₂ therapy is interrupted due to surgery. Details of its manufacture and control are cross referenced to DMF (b) (4). This was found adequate to support this application (David Claffey, 10 DEC 2013). Manufacturing involves several synthetic steps. Two genotoxic impurities are controlled at intermediate (b) (4) and the bulk of the remaining impurities and residual reagents and solvents are controlled at drug substance release. The drug substance release specification was adequately justified in DMF (b) (4). The drug substance is stored at (b) (4). Data were provided to support the proposed retest date.

Drug product: The drug product will be supplied as a sterile lyophilized (b) (4) in single-use glass vial. Each vial is designed to deliver 50 mg of cangrelor (based on free acid) in 10 ml (b) (4) clear glass vials fitted with grey 20 mm (b) (4) rubber stopper and sealed with 20 mm aluminum 'flip-off' overseal. The vial contains a target (b) (4) mg of cangrelor tetrasodium (this amount includes both the sodium ion and a (b) (4) overage). Cangrelor is intended for intravenous administration after reconstitution with 5ml sterile

Executive Summary Section

water for injection. The only excipients are mannitol and sorbitol. The proposed commercial formulation and single 50 mg strength was used for all the Phase III studies. The clinical product was manufactured at two sites, (b) (4) from lots of drug substance manufactured at (b) (4). The commercial product will be manufactured at (b) (4). The manufacturing process is typical for a lyophilized IV-administered product. The lyophilization process was designed to product a stable (b) (4) which is can be stored at room temperature. Studies to demonstrate the compatibility of cangrelor with the infusion solutions were found to be adequate after additional studies were conducted at Agency request. The in-use expiry periods are limited by the results of microbial stability studies which support a 12 hour expiry period in D5W and 24 hours in saline. Drug interaction studies found cangrelor formed a precipitate with 18 out of 101 drug solutions tested. These incompatible drugs are listed in the proposed label. The drug product specification is typical for an intravenously administered product.

Data were provided from eight registration lots – three from (b) (4), three from (b) (4) and two from the (b) (4), the proposed commercial site. Data up to 48 months were provided for the non-commercial sites and results through six months were provided for the commercial site. Accelerated data through six months were provided for each of the eight batches. All results remained within specified limits with no trends apparent apart from the (b) (4) and minor increase in total impurities. Few differences were apparent between batches or manufacturing sites – except for the slower reconstitution time from the lots originating from the (b) (4) site. The proposed (b) (4) months data is supported by real time data from four lots (two from each of the initial sites). Each of these were pilot scale batches. Although only six months data were provided from the proposed commercial site, the applicant states that the manufacturing process were identical

B. Description of How the Drug Product is Intended to be Used

The drug product is intended for IV administration over two hours for PCI and up to 24 hours for bridging after reconstitution in 5.0 ml SWFI then dilution in 250 ml saline or D5W. Reconstituted drug can be stored up to 12 hours in D5W and 24 hours in saline.

C. Basis for Approvability or Not-Approval Recommendation

The data provided in this application and the referenced DMFs were found acceptable from a CMC perspective. An approval recommendation is contingent upon an acceptable recommendation from CDER OC - which is pending at time of completion of this review.

44 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

DAVID J CLAFFEY
12/12/2013

OLEN M STEPHENS
12/12/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: David Claffey, CMC Reviewer
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: david.claffey@fda.hhs.gov
Phone: (301)-796 1343
Fax: (301)-796- 9747

FROM: FDA
Division of Pharmaceutical Analysis
Michael Trehay, MVP Coordinator
645 S Newstead Avenue
St. Louis, MO 63110
Phone: (314) 539-3815

Through: John Kauffman, Deputy Director
Phone: (314) 539-2168

SUBJECT: Methods Validation Report Summary

Application Number: 204958

Name of Product: (b) (4) (cangrelor) for injection, 50 mg/10mL vial

Applicant: The Medicines Company

Applicant's Contact Person: Stephen Sherman, Sr. Director of Global Regulatory Affairs

Address: Stephen Sherman, Sr. Director of Global Regulatory Affairs

Telephone: (973) 290-6300 Fax:

Date Methods Validation Consult Request Form Received by DPA: 6/19/13

Date Methods Validation Package Received by DPA: 6/19/13

Date Samples Received by DPA: 9/12/13

Date Analytical Completed by DPA: 11/5/13

Laboratory Classification: 1. Methods are acceptable for control and regulatory purposes.
2. Methods are acceptable with modifications (as stated in accompanying report).
3. Methods are unacceptable for regulatory purposes.

Comments: Summary of results is attached. Analyst's work sheets and chromatograms are available at
<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f88054a6f0>



Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
St. Louis, MO 63101
Tel. (314) 539-3815

Date: November 6, 2013
To: David Claffey, CMC Reviewer
Through: John Kauffman, Deputy Director, Division of Pharmaceutical Analysis
From: Michael Trehy, Analyst
Subject: Method Validation for NDA 204958
(b) (4) (cangrelor) for injection, 50 mg/10 mL vial

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

1. Assay for Degradation Products in Cangrelor for Injection (HPLC)

The following methods were evaluated and are acceptable for quality control and regulatory purposes with modification:

1. Identification, Assay and Content Uniformity for Cangrelor in Cangrelor for Injection by HPLC

The applicant determines the assay percent using the (b) (4) 10 mL vial. DPA agrees that the calculation for assay and content uniformity is correct for time of release analysis. DPA suggests that for shelf-life analysis the measured mg/10 mL vial should be divided by the label claim which is 50 mg/10 mL vial rather than by (b) (4) mg/10 mL vial as shown in the calculation. This would result in (b) (4) % label claim at the time of release, which is within the specification limits.

Link to analyst's work sheets and chromatograms
<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f88054a6f0>

Summary of Results

NDA 204958

Identification, Assay and Content Uniformity for Cangrelor in Cangrelor for Injection by HPLC

Identification

UV spectrum: Observed spectrum has two absorbance maxima at (b) (4) nm.

Specification: The spectra from the sample preparation are comparable to the spectra from the reference standard with absorbance maxima at (b) (4) nm and (b) (4) nm. Passed

Retention time: (b) (4) % difference in retention time from sample to standard

Limit (b) (4) %. Passed

Assay by HPLC (b) (4) mg/10 mL vial)

Assay 1: (b) (4) Assay 2: (b) (4) Average (2) (b) (4) (b) (4) %

Limit

Passed

Content Uniformity HPLC (b) (4) mg/10 mL vial)

(b) (4) % avg(3) = (b) (4) % acceptance value = (b) (4)

Passed

Assay for Degradation Products in Cangrelor for Injection (HPLC)

Degradation Products

Average results for 3 samples tested						
area sum = sum of all peaks with area \geq (b) (4) % of the area for cangrelor						
area % = peak area/area sum * 100						
Peak ID	AVG-RT	RRT	area %	limit		
unknown	(b) (4)	(b) (4)	(b) (4)	(b) (4)	passed	
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	passed	
unknown	(b) (4)	(b) (4)	(b) (4)	(b) (4)	passed	
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	passed	
unknown	(b) (4)	(b) (4)	(b) (4)	(b) (4)	passed	
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	passed	
unknown	(b) (4)	(b) (4)	(b) (4)	(b) (4)	passed	
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	passed	
area sum = (b) (4) %					\leq (b) (4) %	passed

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/s/

MICHAEL L TREHY
11/07/2013

JOHN F KAUFFMAN
11/07/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION CONSULT REQUEST FORM

TO: FDA
Division of Pharmaceutical Analysis
Attn: Michael Trehy
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: David Claffey, CMC Reviewer
Kasturi Srinivasachar, CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: david.claffey@fda.hhs.gov
Phone: (301)-796 1343
Fax.: (301)-796 9747

Through: Ramesh Sood, Branch Chief
Phone: (301)-796 1466
and
ONDQA Methods Validation Project Manager
Phone: (301)-796 1926

SUBJECT: Methods Validation Request

Application Number: NDA 204958

Name of Product: (b) (4) (cangrelor) for injection, 50 mg/10mL vial

Applicant: The Medicines Company

Applicant's Contact Person: Stephen Sherman, Sr. Director of Global Regulatory Affairs

Address: 8 Sylvan Way, Parsippany, NJ 07054

Telephone: 973-290 6300 Fax: Not available

Date NDA Received by CDER: **4-30-13**

Date of Amendment(s) containing the MVP: **4-30-13**

DATE of Request: **6-18-13**

Requested Completion Date: **9-18-13**

PDUFA User Fee Goal Date: **4-30-14**

Submission Classification/Chemical Class: NME

Special Handling Required: No

DEA Class: N/A

Format of Methods Validation Package (MVP)

Paper Electronic Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

All information relative to this application is to be held confidential as required by 21 CFR 314.430.

MVP Reference #	METHODS VALIDATION REQUEST			NDA # 204958
⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT				
ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION		
Reference Standard	500 mg	(b) (4) .08.601		
Cangrelor for Injection	150 vials (50mg/vial)	00001		
(b) (4) (b) (4) reference material	50 mg	TBD		
(b) (4) (b) (4) reference material	50 mg	TBD		
⇒ ITEM 2: Contents of Attached Methods Validation Package				Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)				3.2.P.1.
Specifications/Methods for New Drug Substance(s)				2.3.S.4.1
Specifications/Methods for Finished Dosage Form(s)				3.2.P.5.1/3.2.P.5.2
Supporting Data for Accuracy, Specificity, etc.				3.2.P.5.3
Applicant's Test Results on NDS and Dosage Forms				3.2.R.2.1
Other: MVP				3.2.R.2
⇒ ITEM 3: REQUESTED DETERMINATIONS Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.				
Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
Drug Product	ID, Assay and Content Uniformity by HPLC	3.2.R.2.1/ Table 1	0	No method number given Validation Report in 3.2.P.5.3
Drug Product	Assay of Degradation Products by HPLC	3.2.R.2.1/ Table 1	0	No method number given Validation Report in 3.2.P.5.3

Additional Comments:

Methods Validation Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method)

6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason

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/s/

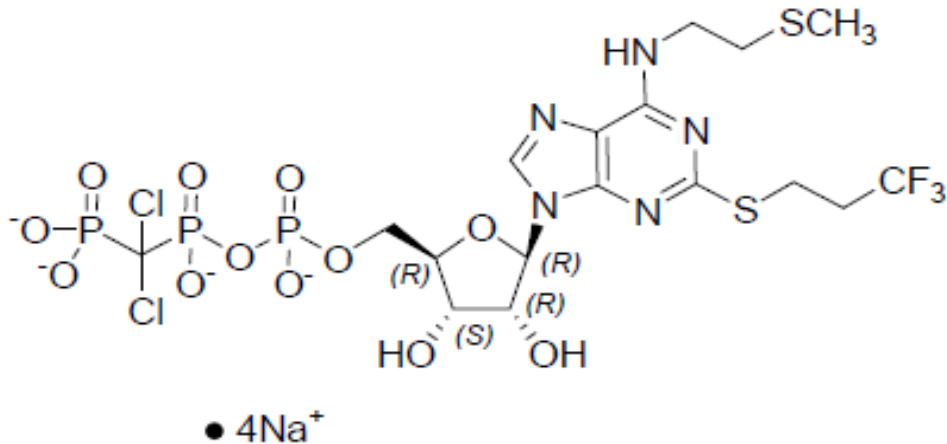
KASTURI SRINIVASACHAR
06/18/2013

RAMESH K SOOD
06/19/2013

YOUBANG LIU
06/19/2013

Initial Quality Assessment
Branch I

OND Division:	Division of Cardiovascular and Renal Products
NDA:	204958
Applicant:	The Medicines Co.
Letter Date:	30 April 2013
Status Date:	30 April 2013
PDUFA Date:	TBD
Tradename:	(b) (4) (proposed)
Established Name:	Cangrelor
Dosage Form:	Sterile lyophilized Powder for (b) (4), 50 mg in 10 mL vial
Route of Administration:	IV
Indication:	Reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention
Assessed by:	Kasturi Srinivasachar
ONDQA Fileability:	Yes



In the figure (R) or (S) denotes the configuration of each chiral center

Summary

This is a 505(b)(1) e-CTD NME NDA for cangrelor, a new direct acting P2Y₁₂ receptor antagonist that blocks adenosine diphosphate induced platelet activation and aggregation. It is stated that cangrelor, administered intravenously provides fast-onset, potent and consistent P2Y₁₂ inhibition, with reversible binding and a half-life of 3-6 minutes. Clinical development of cangrelor was carried out under IND 56812. There have been no CMC specific meetings with the Applicant and only one CMC issue was brought up in a multidisciplinary pre-NDA meeting held on 20 Nov. 2012. This concerned the extent of stability data that would be provided in the NDA both from registration batches at non-commercial sites and representative commercial scale batches from the proposed commercial manufacturing site. They were informed that their product stability proposal was reasonable and the shelf-life would be determined during NDA review. The tradename (b) (4) has been proposed but not yet assessed by DMEPA.

Drug Substance

Cangrelor tetrasodium is a white to off-white solid which decomposes above 200°C. It is very water soluble but insoluble in ethanol and acetone at ambient temperature. It is a synthetic adenosine derivative with 4 chiral carbons which are derived from the starting material, (b) (4). Crude cangrelor tetrasodium is synthesized in 7 stages involving only (b) (4).

The drug substance is (b) (4). The drug substance was first developed and manufactured by AstraZeneca and used in toxicology, Phase 1 and Phase 2 studies. (b) (4) was the manufacturer for Phase 3 studies and will also be the commercial supplier. The manufacturing process was (b) (4).

Related substances are determined by HPLC and ion chromatography methods. The specification includes tests for bacterial endotoxins, microbial limits and the absence of specified microorganisms. Data have been submitted for Phase 3 clinical and registration batches (b) (4) as well as earlier batches manufactured by AstraZeneca for Phase 1 and 2 and toxicology studies.

Stability data are provided in the DMF but summarized in the NDA. 36 months of long-term stability data are available under frozen storage conditions (b) (4) for 4 primary and 1 supportive batches of cangrelor tetrasodium. The batches were packaged (b) (4).

A retest date of (b) (4) months is proposed. It is stated that the drug substance (b) (4).

All CMC information for cangrelor tetrasodium is referenced to DMF (b) (4) held by the manufacturer, (b) (4). However, a summary of the information is provided in Module 2, QOS. DMF (b) (4) was initially submitted in June 2005 and neither the original submission nor subsequent amendments have been reviewed.

Drug Product

Cangrelor for injection is a 50 mg sterile lyophilized (b) (4) in a 10 mL single-use glass vial. It is intended for IV use after reconstitution with 5 mL sterile water for injection. Compendial grade mannitol, sorbitol, sodium hydroxide and water for injection are the excipients used in the formulation. Mannitol (b) (4) and sorbitol (b) (4). pH is adjusted with sodium hydroxide. In addition, (b) (4)

(b) (4) Phase 2 clinical trial formulations were manufactured in the pilot manufacturing area at AstraZeneca, UK. The drug product used in Phase 3 trials was manufactured at two sites, (b) (4). The commercial manufacturing and primary packaging of Cangrelor for Injection will be performed at (b) (4)

A lyophilized dosage form was chosen for this product in view of the long term instability of the drug substance in aqueous solution. The manufacturing process at the (b) (4) sites is essentially the same as at the (b) (4) commercial site except for an (b) (4)

(b) (4) The proposed commercial manufacturing process starts with (b) (4)

The proposed specifications cover the standard tests for a lyophilized sterile dosage form i.e. reconstitution time and content uniformity in addition to assay, description, pH, (b) (4), identification, degradation products, particulate matter, endotoxins and sterility. Batch analysis data have been provided for 8 primary stability batches manufactured from 3 different sites including the proposed commercial manufacturing site. Stability data have been submitted for these batches under ICH long term and accelerated storage conditions. 48 months of long term data are provided for 4 registration batches and up to 36 months and 24 months of data, respectively, are available for 2 additional batches. A shelf-life of (b) (4) months is proposed. In-use stability studies have been performed since this is a lyophilized product which is reconstituted with sterile water for injection and further diluted with either 5% dextrose or 0.9% sodium chloride in IV bags. It is proposed that the reconstituted solution in the vial and in the bag may be used up to (b) (4) at room temperature.

Critical Review Issues

Drug Substance

- An in-depth review of DMF (b) (4) including the original submission and subsequent amendments, should be carried out paying particular attention to chirality issues (maintaining chirality during the manufacturing process), strategy for the control of potentially genotoxic impurities, purification procedures, including reprocessing, specifications for the starting materials and intermediate etc.
- It is stated that potentially genotoxic impurities are controlled at the intermediate (b) (4) and that the limits established at this stage would ensure that the levels in the drug substance do not exceed (b) (4) µg / day. It should be noted that these impurities are all (b) (4) and presumably exert their toxicity by the same mechanism. Consequently, (b) (4) µg / day is the maximum permissible for the total of all potentially genotoxic impurities in the drug substance and not for individual impurities. Since these are not tested in the drug substance, are the acceptance criteria in (b) (4) appropriate?
- Regarding Specifications
 - Are the limits for (b) (4) adequately justified? Is a Pharm/Tox consult needed?
 - Is the (b) (4) level proposed (\leq (b) (4) %) acceptable?

Drug Product

- Since this is a sterile lyophilized powder for (b) (4), the major critical issues are the sterile manufacturing process, sterility assurance of the product after manufacture and maintenance of sterility over the shelf-life. These aspects are expected to be covered by the microbiology reviewer.
- Is a (b) (4) % overage of the drug substance in the formulation acceptable?
- Is a bulk hold time of (b) (4) hrs acceptable given the solution instability of cangrelor?
- Is the manufacturing process, including the lyophilization cycle, described in adequate detail?
- It is stated that cangrelor for injection is compatible with either 5% dextrose injection or 0.9% sodium Chloride injection in IV bags at room temperature for up to (b) (4) hrs in a concentration range of 0.1 mg/mL to 1.0 mg/mL. Were these studies done on aged samples which were close to the proposed expiration date?
- Regarding the UV ID test in the specification, shouldn't the maximum peak wavelengths be listed in the acceptance criteria instead of "conforms"?
- Can a (b) (4) month expiration dating period be granted even without considering the data generated at (b) (4) which has continuing cGMP problems?
- The stability protocol for annual batches includes a footnote stating that 3, 6, 9 and 18 month time points may be eliminated after a significant body of data (i.e. 5 years of commercial experience) are available. Is this acceptable?

Labeling

- Although the free acid, cangrelor, is correctly used as the nonproprietary name (amendment dated 5-15-2013) and the strength is based on this, the equivalency

- statement to the sodium salt is missing from the container labels. Refer to MAPP 5021.1.
- The NDC number is missing in the How Supplied section of the PI

Comments and Recommendations: The NDA is fileable – see attached filing check list. Facilities have been entered into EES. The reviewer should verify the completeness of the entries. Methods validation will be requested shortly since this is an NME -- Drug Product: Identification, Assay and Content Uniformity by HPLC and Degradation Products by HPLC. Other methods, e.g. for drug substance, may be requested by the reviewer at a later date, if warranted on the basis of the DMF review. A categorical exclusion from Environmental Assessment has been requested. A single CMC reviewer is recommended since a major portion of the drug product information will be reviewed by the microbiology reviewer.

Kasturi Srinivasachar
CMC Lead
Ramesh Sood
Branch Chief

May. 31, 2013
Date
May. 31, 2013
Date

PRODUCT QUALITY -- CMC and BIOPHARMACEUTICS
FILING REVIEW FOR NDA

NDA Number: 204958 **NDA Type:** 1 **Established/Proper Name:** (b) (4) (cangrelor)

Applicant: The Medicines Company **Letter Date:** Apr 30, 2013 **PDUFA Goal:** TBD

Stamp Date: Apr 30, 2013

CMC Reviewer: David Claffey

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		
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* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical exclusion requested

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		Cross-reference to DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Cross-reference to DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Cross-reference to DMF (b) (4)
15.	Does the section contain controls for the DS?	X		Cross-reference to DMF (b) (4)
16.	Has stability data and analysis been provided for the drug substance?	X		Cross-reference to DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		No master batch record
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any Comparability Protocols been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		Drug Product methods only

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	X		

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		LoA to DMF (b)(4) for DS and DMFs for vial and stoppers

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		Fileable for Product Quality. See Biopharmaceutics Filing Review for fileability of the Biopharm Section
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			NA
36.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			See Biopharm filing review
37.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	

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/s/

KASTURI SRINIVASACHAR
05/31/2013

RAMESH K SOOD
05/31/2013