

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204958Orig1s000

OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	Robert Temple, MD
Subject	Deputy Office Director Decisional Memo
NDA/BLA # Supplement #	204958
Applicant Name	The Medicines Company
Date of Submission	December 23, 2014
PDUFA Goal Date	June 23, 2015
Proprietary Name / Established (USAN) Name	KENGREAL / cangrelor
Dosage Forms / Strength	Single-use 10 ml vial containing 50 mg cangrelor as a lyophilized powder for reconstitution
Proposed Indication	<p>KENGREAL is an intravenous P2Y₁₂ platelet inhibitor indicated for the reduction of thrombotic cardiovascular events in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) (b) (4)</p> <p>[REDACTED]</p> <p>KENGREAL 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.</p>
Action:	Approval
Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Fred Senatore, Nhi Beasley
Statistical Review	Jialu Zhang
Pharmacology Toxicology Review	Belay Tesfamariam
CMC Review	Wilson-Lee, Eradi, Shanks
Microbiology Review	Steven P. Donald
Clinical Pharmacology Review	Sreedharan Sabarinath
OSI	Sharon Gershon
CDTL Review	Stephen Grant

OND=Office of New Drugs
 OPDP=Office of Prescription Drug Products
 OSI=Office of Scientific Investigations
 CDTL=Cross-Discipline Team Leader
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DRISK=Division of Risk Management

I. Introductionⁱ

Cangrelor is a parenterally administered platelet P2Y₁₂ inhibitor with rapid onset and offset of the same platelet-inhibiting effect as clopidogrel, prasugrel, and ticagrelor. Its proposed use and the use studied in the PHOENIX study, which is intended to support approval, is as treatment for patients with coronary artery disease [REDACTED] (b) (4)

[REDACTED] who are undergoing percutaneous coronary intervention (PCI), and who have not received a glycoprotein IIb/IIIa inhibitor or an oral P2Y₁₂ platelet inhibitor [REDACTED] (b) (4). It was studied in PHOENIX as an alternative to clopidogrel taken at the time of PCI. In PHOENIX, patients were randomly assigned to clopidogrel 300 mg or 600 mg (investigator discretion) or to an infusion of ticagrelor taken for two hours or until PCI was completed. Clopidogrel 600 mg was given to ticagrelor patients after the drug was stopped.

The rationale for this use is two-fold:

1. Most of the ischemic events associated with acute coronary syndrome (UA, NSTEMI, STEMI) occur early and clopidogrel takes at least 2 hours to be effective, even when a 600 mg dose (greater than the 300 mg used for clopidogrel approved claims) is used. A rapidly-acting drug could reduce these early ischemic events compared to clopidogrel started at the time of PCI. Note that such a potential benefit might be smaller, if present at all, if the anti-platelet drug used were prasugrel or ticagrelor, because these drugs exert their platelet-inhibiting effects more rapidly than clopidogrel and that no benefit would be expected if clopidogrel were given well before PCI.
2. Because PCI or the angiography that precedes it can sometimes lead to the need for a coronary artery bypass grafting (CABG) operation, a procedure in which the

presence of anti-platelet drugs could cause excessive bleeding, there is some reluctance to use an oral, long acting anti-platelet drug before the coronary anatomy is defined and before PCI is started. The rapid reversibility of cangrelor given at the time of PCI is therefore desirable.

It is important to note that the circumstances in which cangrelor's benefit has been shown are relatively narrow:

1. The drug for which cangrelor was substituted was clopidogrel, not prasugrel or ticagrelor (cangrelor causes platelet inhibition more rapidly than either of those drugs but in studies in acute coronary syndrome (ACS) both drugs were superior to clopidogrel in the early period, so that cangrelor might have less or no advantage). It remains true, however, as noted, that there can be reluctance to use any anti-platelet drug with longer effects early in PCI, in case a surgical procedure is needed.
2. Patients did not receive glycoprotein IIb/IIIa inhibitors, which work rapidly. Again, however, these drugs are often not used in this setting.

(b) (4)

The PHOENIX study tested cangrelor, as Dr. Grant explains, in a setting that made it possible to show a benefit:

1. No pre-PCI use of any anti-platelet drug.
2. More patients with stable coronary disease, a group, as Dr. Grant notes, without baseline elevations of markers of cardiac necrosis, so that the data would be less "noisy," making it more possible to detect increases arising from PCI.

A Complete Response (CR) letter was sent to the Medicines Company on April 30, 2014. It expressed several concerns, all enumerated by Dr. Grant and discussed by him.

The Medicines Company responded to the CR letter on December 23, 2014, and it has been reviewed by Drs. Senatore and Beasley, Dr. Zhang, Dr. Sabarinath, and Dr. Grant, all of whom agree that the application should be approved. The Cardiovascular and Renal Drugs Advisory Committee met on April 15, 2015 voting 9-2 that cangrelor should be approved. I have little to add to Dr. Grant's discussion of database unlocking, bioequivalence, or differences between site-reported and adjudicated events. Drs. Senatore and Zhang have also addressed these issues. All agree that these are not issues that would call the favorable results of PHOENIX into question. I will, however, address the two points that we indicated in the CR letter most directly question the effectiveness of cangrelor: 1) the components of the primary endpoint, some of which might not represent effects whose reduction would be of value and 2) whether clopidogrel use in stable angina should be delayed until PCI when it could be given much earlier (it was the delayed use that allowed a possible advantage for cangrelor).

II. Meaningful Endpoint

The protocol-specified endpoint was a composite of death, MI, ischemic driven revascularization, and stent thrombosis over 48 hours. The endpoint included two components of uncertain significance: 1) cases of stent thrombosis that were Intra-Procedural Stent Thrombosis (IPST), an outcome not considered evidence of effectiveness in the past, and 2) many cases of MI with very modest CK-MB elevations (3-10x ULN), again an outcome of uncertain meaning. At our request an analysis removing IPST and MIs with CKMD < 10x ULN was carried out, with the results shown in the reviews of Drs. Zhang and Grant.

Endpoint	Cangrelor	Clopidogrel	OR	P
Death/MI/IDR/ST (primary endpoint)	257 (4.7)	322 (5.9%)	0.78 (0.66, 0.93)	0.005
Death/SCAI/MI/IDR, ARC-ST (revised endpoint)	79 (1.4%)	114 (2.1%)	0.69 (0.52, 0.92)	0.011
IDR = ischemic-driven revascularization ST = stent thrombosis SCAIMI = Soc for CV Angiography: CK > 10xULN (see Senatore) ARC-ST = Academic Research Consortium Stent Thrombosis (see Senatore's review, p 39)				

Removal of these clinically questionable endpoints thus led to a numerically stronger (lower OR) finding, still highly nominally significant. Dr. Grant notes that this single study, with a relatively low p-value showing an advantage over an active anti-platelet treatment, is persuasive and that the Division had agreed with the applicant during the IND process that a single strong study would support approval.

III. Use of clopidogrel in Stable Angina

Clearly, patients with angina could be given clopidogrel weeks to hours before PCI, attaining the full effect of clopidogrel before the procedure and eliminating need for cangrelor. The avoidance of cangrelor also would eliminate the post-cangrelor period, when another anti-platelet drug must be started, but where, at least for clopidogrel or prasugrel, there is a potentially troublesome period (1-2 hours) of diminished platelet inhibition.

Whether the approach is ideal can be debated, but there is no doubt that it is common practice to delay platelet inhibition until after angiography, at about the time of initiation of PCI. The review team considers this an acceptable approach, as Dr. Grant states, and the Advisory committee also did not consider it inappropriate. If that approach is used, particularly with clopidogrel as the anti-platelet drug, cangrelor would be expected to provide a benefit, namely, a reduced rate of thrombotic outcome events, which has been demonstrated. The earlier full anti-platelet effect also would be expected to increase bleeding. As Dr. Grant explains in his safety analysis, non-CABG 48 hour bleeding events were in fact increased, but there were few severe bleeds.

IV. Post-Cangrelor Period

As noted, and as will be explained in labeling, using a figure in Dr. Grant's and Sabarinath's reviews, stopping cangrelor and resuming oral anti-platelet therapy leaves a window period of less than full platelet inhibition, at least 2 hours for clopidogrel 600 mg, and 1.5-2 hours for prasugrel, but much less time for ticagrelor, which could be started during the cangrelor infusion, as cangrelor does not block ticagrelor's effect. Labeling will show the more rapid platelet inhibition if a drug other than clopidogrel is used.

Nonetheless, even for clopidogrel, the drug used in PHOENIX, there were relatively few "extra" events in the 2-4 or 2-6 hours after cangrelor was stopped. These are shown in Dr. Grant's memo (p 9). Composite events in the cangrelor group vs clopidogrel group were 12 vs 12 in hours 2-4 and 26 (cangrelor group) vs 21 (clopidogrel group) in hours 2-6, reflecting the fact that most events in the study occurred early in the PCI treatment period. During the first 2 hours results favored cangrelor more strongly, 50 vs 88 (OR < 0.6), than did the primary endpoint.

V. Conclusion and Risk-Benefit Assessment

I agree with the conclusions of the review team and Dr. Grant that cangrelor should be approved for use as an adjunct to PCI to reduce the risk of periprocedural MI, repeat coronary vascularization, or stent thrombosis in patients not previously treated with a P2Y₁₂ platelet inhibitor and not receiving a glycoprotein IIb/IIIa inhibitor. This benefit was shown in the PHOENIX trial and was not associated with an unacceptable increase in bleeding. When cangrelor is stopped (after about 2 hours) oral anti-platelet therapy should be initiated (could be clopidogrel, prasugrel or ticagrelor, although only clopidogrel was studied).

As indicated above (Section II), concerns about the meaningfulness of the original composite endpoint, an important component of our Complete Response Letter, were resolved by an

analysis that removed IPST and very small MIs (CK-MB elevation < 10x ULN). Dr. Grant urged that this analysis, although it supported the primary analysis, not be included in Section 14 (Clinical Studies) of labeling. Although I appreciate concerns with “post-facto” analyses, I believe it should be included in the labeling in this case. The analysis follows a successful primary analysis, so it is not an analysis that “saves” a failed study. Rather it is a response to significant concerns expressed by the Advisory Committee as well as some reviewers about components of the primary endpoint. It also informs any risk-benefit assessment.

ⁱ Also see previous Deputy Director memo of April 30, 2014 for further background and Dr. Grant’s detailed Deputy Division Director review.

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/s/

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06/22/2015

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