KENGREAL®
(cangrelor) for injection

Reimbursement Guide Executive Summary

Coverage of KENGREAL® (cangrelor) for Injection

Setting of care and payer policy generally determines whether KENGREAL® will be reimbursed separately.

KENGREAL® used in:	Separately reimbursed	Bundled (not separately reimbursed)
Inpatient Setting		Medicare—yes Other payers—typically
Outpatient Setting	Medicare—yes Other payers—varies	

Hospital Inpatient Coverage of KENGREAL®: Medicare uses MS-DRGs (Diagnosis Related Groups) to determine the amount of fixed payments to pay hospitals for an inpatient admission. KENGREAL® reimbursement is included under the MS-DRG payment in the inpatient setting. Other payers may also make fixed payments similar to MS-DRG reimbursement, dependent on payer or local contracts, or follow another methodology such as per diem or percent of charges payment.

Hospital Outpatient Coverage of KENGREAL®: For Medicare, when used as part of a hospital outpatient PCI procedure, reimbursement for KENGREAL® will be separate from the Comprehensive APC payment received for the outpatient PCI procedure. Other payers may follow a similar payment methodology as Medicare, depending on the payer and the local contracts.

Healthcare Common Procedure Coding System (HCPCS) Codes

Following are the drug codes and billing units for KENGREAL®.

Medicare usually prefers the use of C-codes in the Hospital Outpatient setting, unless or until a drug receives a drug-specific J-code.

Some private payers and Medicaid programs accept C-codes, but many prefer the use of miscellaneous J-codes. Medicare, state Medicaid programs, and many private payers require UB-04 (CMS-1450) claim forms for the Hospital Outpatient setting. The following codes and suggested billing units may be used consistent with payer requirements and individual patient circumstances:

Setting	HCPCS	Billing Description	Billing Unit	Hospital Outpatient Rate
Hospital Outpatient (Medicare and some commercial payers)	C9460	Injection, Cangrelor, 1 mg	50 Units	106% ASP*
Hospital Outpatient (for commercial payers that do not accept C-codes)	J3490	Unclassified Drug Codes	1 Unit	106% ASP*

*Does not include impact of sequestration required by the Budget Control Act of 2011. The effective payment rate for separately covered drugs, including KENGREAL®, is typically 104.3% of ASP.

Medicare coding guidance calls for a billing unit of "1" to be used with "Unclassified Drug" HCPCS codes, like J3490. The billing unit used with the "Unclassified Drug" HCPCS codes may, however, vary by payer (e.g., mg or each, etc.). In fact, some Medicare Administrative Carriers (MACs), Medicaid programs, and private payers prefer that the billing unit not reflect a predetermined unit of "1", but instead, reflect the actual number of the most relevant unit actually administered to that patient in connection with services. We anticipate that payers adopting this approach will wish to receive claims for the number of milligrams administered to the patient. Accordingly, Healthcare Professionals should contact payers directly to verify the billing unit deemed most appropriate by the payer.

Accurate reporting of the miscellaneous J-code, as well as the quantity of KENGREAL® administered to each patient, is critical for appropriate and timely reimbursement. When completing a UB-04 (CMS-1450) claim form for KENGREAL® using a miscellaneous J-code and default billing unit of "1" in Field 46, it is important to consider including in the "Remarks" section the following information:

1. The National Drug Code (NDC 65293-003-01);
2. Quantity of KENGREAL® administered, expressed in the unit of measure deemed most appropriate by the payer (e.g., mg); and
3. Date that KENGREAL® was furnished to the patient.

See Important Safety Information on reverse and accompanying Full Prescribing Information.

For more information, please visit Kengreal.com.

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KENGREAL®
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For payers that expect the actual amount of product administered to be listed in the UB-04 (CMS-1450) claim form in Field 46, the following information should be considered for inclusion in the "Remarks" section:

1. National Drug Code (NDC 65293-003-01);
2. Date that KENGREAL® was furnished to the patient.

At the time the claim form is submitted or thereafter, some payers may also require prescribing information, FDA-approval letter, support of medical necessity and a drug purchase invoice.

Because KENGREAL® is available in single use vials, there will be circumstance where less than the full vial will be administered to the patient, the unused portion of the drug, which must be discarded, may be billed for reimbursement. Rules governing the billing requirements for unused amounts vary by payer. For example, some MACs may require the use of the "JW" modifier to bill for unused and discarded portions of single use vials. Healthcare Professionals should contact payers directly to verify the appropriate billing requirements.

Importance of Reporting KENGREAL® in Claim Form Submissions: It is important for hospitals to continue to code for KENGREAL® regardless of separate reimbursement to ensure costs are reflected in future reimbursements. Although some payers, may not, at least in some sites of service, separately reimburse for KENGREAL®, it is extremely important that providers include KENGREAL® in their claim form submissions, consistent with payer guidance. The reason for this is that many payers use this claim information in setting packaged reimbursement in hospital inpatient, outpatient, or other services. If applicable payer does not have data available in its system to recognize appropriately the cost associated with KENGREAL®, provider reimbursement will be negatively affected.

Prior Authorization and Patient Responsibilities: Some payers may require that a provider obtain prior authorization before the use of KENGREAL®. Further, some payers may require that a provider utilize an alternative therapy for a particular patient; such requirements may be based on the cost of KENGREAL® or an individual patient's circumstances. In addition, patients may have differing financial obligations (copayments, deductibles or other cost-sharing) based on the therapy provided. Providers should confirm the applicable payer policies before utilizing KENGREAL® and should consider providing any required advance notice of such policies to patients.

Disclaimer

The use of this guide is strictly for informational purposes, and does not address all situations or all payer's policies and guidance that may apply. The information provided in this guide was obtained from third-party sources and is subject to change without notice as a result of changes in reimbursement laws, regulations, rules and policies. This guide provides a summary of coding, coverage and payment of KENGREAL® for its Food and Drug Administration (FDA) approved uses as indicated in the prescribing information. The information contained in this document is not intended for purposes of providing clinical practice guidelines for use of KENGREAL®. Please see the package insert for more information.

Chiesi USA, Inc. specifically disclaims liability or responsibility for the results or consequences of any actions taken in reliance on information in this guide. Chiesi USA, Inc. cannot guarantee, nor is it responsible for, the payment of any claim. The coding, coverage and payment for KENGREAL® may vary by payer, plan, patient and setting of care. For more information, Healthcare Professionals should check with the applicable payers for specific coding, coverage and payment requirements related to the use of KENGREAL®. It is the sole responsibility of the Healthcare Professional to code properly for KENGREAL® and related services and to ensure the accuracy of all claims used in seeking reimbursement. All services must be medically appropriate and properly documented in the patient's medical records.

Indication

KENGREAL® (cangrelor) for Injection is a $P2Y_{12}$ platelet inhibitor 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.

For more information,
please visit Kengreal.com.

Important Safety Information

KENGREAL® (cangrelor) for Injection is contraindicated in patients with significant active bleeding.

KENGREAL® is contraindicated in patients with known hypersensitivity (e.g., anaphylaxis) to cangrelor or any component of the product.

Drugs that inhibit platelet $P2Y_{12}$ function, including KENGREAL®, increase the risk of bleeding. In CHAMPION PHOENIX, bleeding events of all severities were more common with KENGREAL® than with clopidogrel. Bleeding complications with KENGREAL® were consistent across a variety of clinically important subgroups. Once KENGREAL® is discontinued, there is no antiplatelet effect after an hour.

The most common adverse reaction is bleeding.

Please see accompanying Full Prescribing Information.

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KENGREAL safely and effectively. See full prescribing information for KENGREAL.

KENGREAL® (cangrelor) for injection, for intravenous use
Initial U.S. Approval: 2015

INDICATIONS AND USAGE

KENGREAL is a $P2Y_{12}$ platelet inhibitor indicated as an adjunct to percutaneous coronary intervention (PCI) for reducing the risk of periprocedural myocardial infarction (MI), repeat coronary revascularization, and stent thrombosis (ST) in patients in who have not been treated with a $P2Y_{12}$ platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor. (1)

DOSAGE AND ADMINISTRATION

- KENGREAL is intended for administration via a dedicated IV line, only after reconstitution and dilution. (2.3)
- Administer 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. (2.1)
- To maintain platelet inhibition after discontinuation of KENGREAL infusion, an oral $P2Y_{12}$ platelet inhibitor should be administered. (2.2)

DOSAGE FORMS AND STRENGTHS

Single-use 10 mL vial containing 50 mg KENGREAL as a lyophilized powder for reconstitution (3.0)

CONTRAINDICATIONS

- Significant active bleeding (4.1)
- Hypersensitivity to KENGREAL or any component of the product (4.2)

WARNINGS AND PRECAUTIONS

- Bleeding: Like other drugs that inhibit platelet $P2Y_{12}$ function, KENGREAL can increase the risk of bleeding (5.1)

ADVERSE REACTIONS

The most common adverse reaction is bleeding. (5.1, 6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Chiesi USA, Inc. at 1-888-661-9260 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Clopidogrel: Do not administer during KENGREAL infusion. (7.1)
- Prasugrel: Do not administer during KENGREAL infusion. (7.1)

Revised: 08/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dosage of KENGREAL is a 30 mcg/kg IV bolus followed immediately by a 4 mcg/kg/min IV infusion. Initiate the bolus infusion prior to PCI. The maintenance infusion should ordinarily be continued for at least 2 hours or for the duration of PCI, whichever is longer.

2.2 Transitioning Patients to Oral $P2Y_{12}$ Therapy

To maintain platelet inhibition after discontinuation of KENGREAL infusion, an oral $P2Y_{12}$ platelet inhibitor should be administered. Administer one as described below:

- Ticagrelor: 180 mg at any time during KENGREAL infusion or immediately after discontinuation *[see Clinical Pharmacology (12.2)]*.
- Prasugrel: 60 mg immediately after discontinuation of KENGREAL. Do not administer prasugrel prior to discontinuation of KENGREAL *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*.
- Clopidogrel: 600 mg immediately after discontinuation of KENGREAL. Do not administer clopidogrel prior to discontinuation of KENGREAL *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*.

2.3 Preparation and Administration

KENGREAL is intended for IV administration, after reconstitution and dilution.

Preparation

For each 50 mg/vial, reconstitute by adding 5 mL of Sterile Water for Injection. Swirl gently until all material is dissolved. Avoid vigorous mixing. Allow any foam to settle. Ensure that the contents of the vial are fully dissolved and the reconstituted material is a clear, colorless to pale yellow solution. Reconstitute the vial prior to dilution in a bag. Parenteral drug products should be inspected visually for particulate matter after reconstitution.

Do not use without dilution. Before administration, each reconstituted vial must be diluted further with Normal Saline (Sodium Chloride Injection 0.9% USP) or 5% Dextrose Injection USP.

Withdraw the contents from one reconstituted vial and add to one 250 mL saline bag. Mix the bag thoroughly. This dilution will result in a concentration of 200 mcg/mL and should be sufficient for at least 2 hours of dosing. Patients 100 kg and over will require a minimum of 2 bags.

Reconstituted KENGREAL should be diluted immediately. Diluted KENGREAL is stable for up to 12 hours in 5% Dextrose Injection and 24 hours in Normal Saline at Room Temperature. Discard any unused portion of reconstituted solution remaining in the vial.

Administration

Administer KENGREAL via a dedicated IV line.

Administer the bolus volume rapidly (<1 minute), from the diluted bag via manual IV push or pump. Ensure the bolus is completely administered before the start of PCI. Start the infusion immediately after administration of the bolus *[see Dosage and Administration (2.1)]*.

3 DOSAGE FORMS AND STRENGTHS

For Injection: 50 mg of KENGREAL lyophilized powder in a single-use 10 mL glass vial for reconstitution.

4 CONTRAINDICATIONS

4.1 Significant Active Bleeding

KENGREAL is contraindicated in patients with significant active bleeding *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

4.2 Hypersensitivity

KENGREAL is contraindicated in patients with known hypersensitivity (e.g., anaphylaxis) to KENGREAL or any component of the product *[see Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Bleeding

Drugs that inhibit platelet $P2Y_{12}$ function, including KENGREAL, increase the risk of bleeding.

In CHAMPION PHOENIX bleeding events of all severities were more common with KENGREAL than with clopidogrel *[see Adverse Reactions (6.1)]*. Bleeding complications with KENGREAL were consistent across a variety of clinically important subgroups (see Figure 1).

Once KENGREAL is discontinued, there is no antiplatelet effect after an hour *[see Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are also discussed elsewhere in the labeling:

- Bleeding *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions 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 practice.

The safety of KENGREAL has been evaluated in 13,301 subjects in controlled trials, in whom, 5,529 were in the CHAMPION PHOENIX trial.

Bleeding

There was a greater incidence of bleeding with KENGREAL than with clopidogrel. No baseline demographic factor altered the relative risk of bleeding with KENGREAL (see Table 1 and Figure 1).

Table 1: Major Bleeding Results in the CHAMPION PHOENIX Study (Non-CABG related Bleeding)[a]

CHAMPION PHOENIX	**KENGREAL** (N=5529)	**Clopidogrel** (N=5527)
Any GUSTO bleeding, n (%)	857 (15.5)	602 (10.9)
Severe/life-threatening [b]	11 (0.2)	6 (0.1)
Moderate [c]	21 (0.4)	14 (0.3)
Mild [d]	825 (14.9)	582 (10.5)
Any TIMI bleeding, n (%)	45 (0.8)	17 (0.3)
Major [e]	12 (0.2)	6 (0.1)
Minor [f]	33 (0.6)	11 (0.2)

Abbreviations: GUSTO: Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; TIMI: Thrombolysis in Myocardial Infarction

[a] Safety population is all randomized subjects who received at least one dose of study drug

[b] intracranial hemorrhage or bleeding resulting in substantial hemodynamic compromise requiring treatment

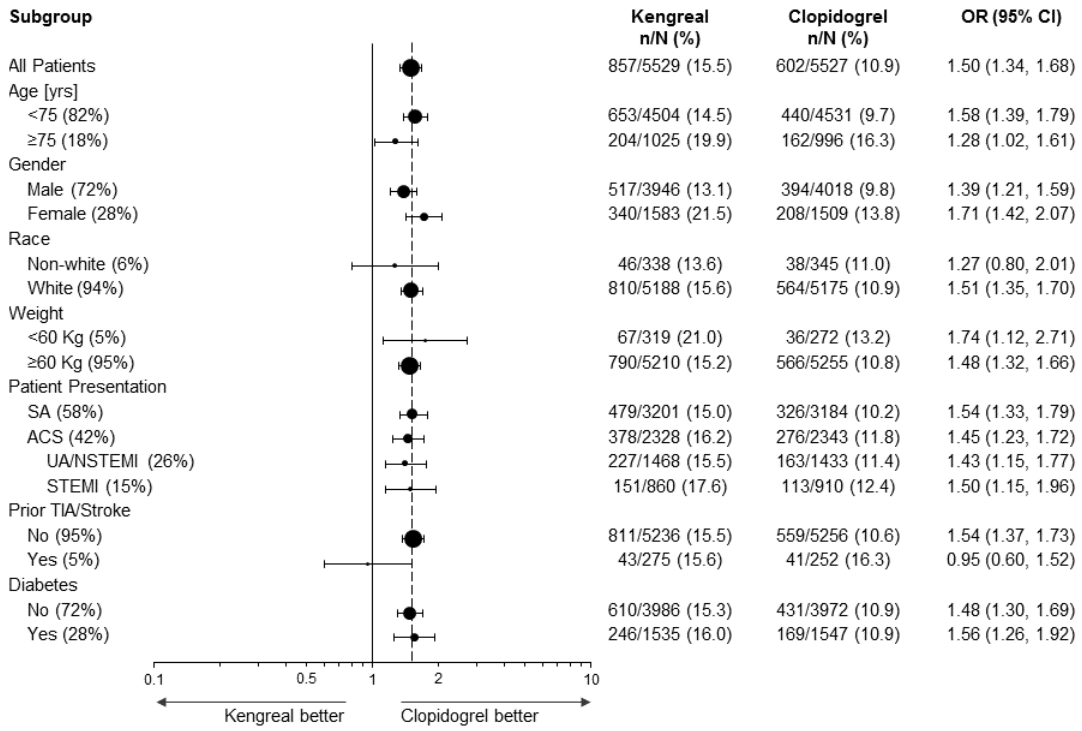
[c] requiring blood transfusion but not resulting in hemodynamic compromise

[d] all other bleeding not included in severe or moderate

[e] any intracranial hemorrhage, or any overt bleeding associated with a reduction in hemoglobin of ≥5 g/dL (or, when hemoglobin is not available, an absolute reduction in hematocrit ≥15%)

[f] any overt sign of bleeding (including observation by imaging techniques) that is associated with a reduction in hemoglobin of ≥3 g/dL and <5 g/dL (or, when hemoglobin is not available, an absolute reduction in hematocrit of ≥9% and <15%)

Figure 1: Bleeding Results in the CHAMPION PHOENIX Study[a] (All Non-CABG related)



[a] Safety population is all randomized subjects who received at least one dose of study drug
Note: The figure above presents effects in various subgroups most of which are baseline characteristics and most of which were pre-specified (patient presentation and weight were not pre-specified subgroups). The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

Drug Discontinuation

In CHAMPION PHOENIX the rate of discontinuation for bleeding events was 0.3% for KENGREAL and 0.1% for clopidogrel. Discontinuation for non-bleeding adverse events was low and similar for KENGREAL (0.6%) and for clopidogrel (0.4%). Coronary artery dissection, coronary artery perforation, and dyspnea were the most frequent events leading to discontinuation in patients treated with KENGREAL.

Non-Bleeding Adverse Reactions

Hypersensitivity

Serious cases of hypersensitivity were more frequent with KENGREAL (7/13301) than with control (2/12861). These included anaphylactic reactions, anaphylactic shock, bronchospasm, angioedema, and stridor.

Decreased renal function

Worsening renal function was reported in 3.2% of KENGREAL patients with severe renal impairment (creatinine clearance <30 mL/min) compared to 1.4% of clopidogrel patients with severe renal impairment.

Dyspnea

Dyspnea was reported more frequently in patients treated with KENGREAL (1.3%) than with control (0.4%).

7 DRUG INTERACTIONS

7.1 Thienopyridines

If clopidogrel or prasugrel are administered during KENGREAL infusion, they will have no antiplatelet effect until the next dose is administered. Clopidogrel and prasugrel, therefore, should not be administered until KENGREAL infusion is discontinued *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of KENGREAL in pregnant women.

Cangrelor did not produce malformations in either the rat or rabbit reproductive studies, and is not considered to be a teratogen.

In embryo-fetal development studies in rats, cangrelor produced dose-related fetal growth retardation characterized by increased incidences of incomplete ossification and unossified hind limb metatarsals at plasma concentration of approximately 5 times lower than that achieved in the PCI setting at the maximum recommended human dose (MRHD). In rabbits, cangrelor was associated with increased incidences of abortion and intrauterine losses, as well as fetal growth retardation at plasma concentrations of approximately 12 times higher than the PCI setting at the MRHD.

8.3 Nursing Mothers

It is not known whether KENGREAL is excreted in human milk.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

In CHAMPION PHOENIX, 18% of patients were ≥75 years. No overall differences in safety or effectiveness were observed between these patients and those patients <75 years *[see Clinical Studies (14.1)]*.

8.6 Renal Impairment

No dosage adjustment is required for patients with mild, moderate, or severe renal impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

KENGREAL has not been studied in patients with hepatic impairment. However, the metabolism of KENGREAL is not dependent of hepatic function, so that dosage adjustment is not required for patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There is no specific treatment to reverse the antiplatelet effect of KENGREAL but the effect is gone within one hour after the drug is discontinued.

In clinical trials, 36 patients received an overdose of KENGREAL, ranging from 36 to 300 mcg/kg (bolus dose) or 4.8 to 13.7 mcg/kg/min (infusion dose). The maximum overdose received was 10 times the PCI bolus dose or 3.5 times the PCI infusion dose in 4 patients. No clinical sequela were noted as a result of overdose following completion of KENGREAL therapy.

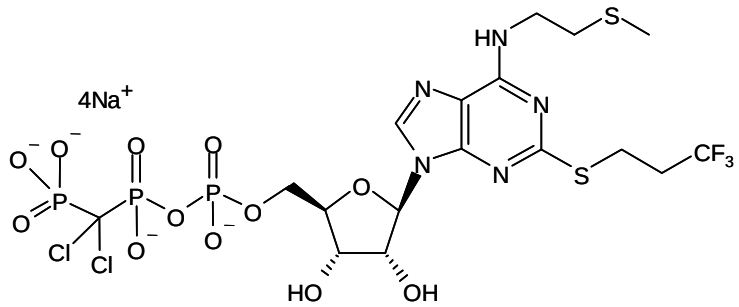
11 DESCRIPTION

KENGREAL is a direct-acting $P2Y_{12}$ platelet receptor inhibitor that blocks adenosine diphosphate (ADP)-induced platelet activation and aggregation. The chemical structure is similar to adenosine triphosphate (ATP).

The chemical name of KENGREAL is tetrasodium salt of N6-[2-(methylthio)ethyl]-2-[(3,3,3,-trifluoropropyl)-5'-adenylic acid, monanhydride with (dichloromethylene) bisphosphonic acid.

The empirical formula of KENGREAL is $C_{17}H_{21}N_5Cl_2F_3Na_4O_{12}P_3S_2$ and the molecular weight is 864.3 g/mol.

The chemical structure is represented below:



Cangrelor for Injection is a sterile white to off-white lyophilized powder for IV infusion. In addition to the active ingredient, cangrelor, each single use vial contains mannitol, sorbitol, and sodium hydroxide to adjust the pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

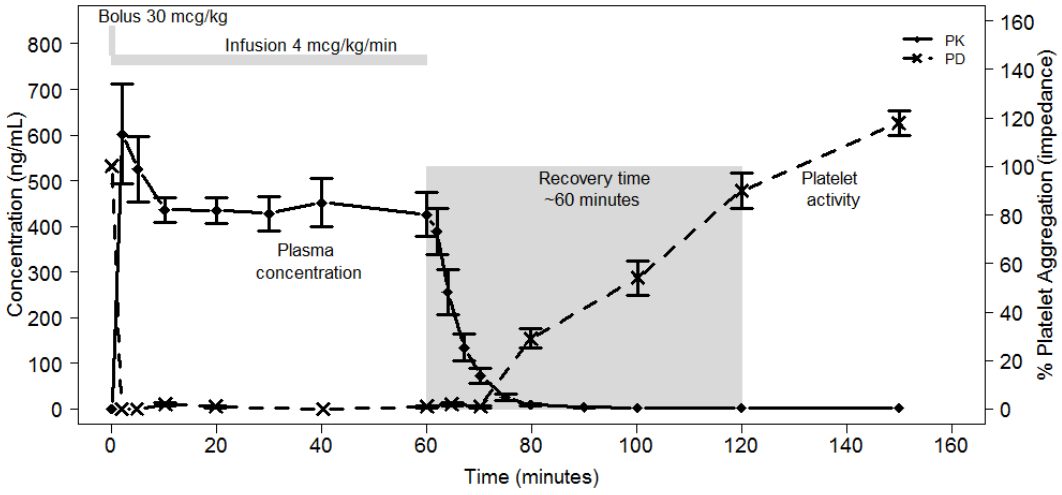
Cangrelor is a direct $P2Y_{12}$ platelet receptor inhibitor that blocks ADP-induced platelet activation and aggregation. Cangrelor binds selectively and reversibly to the $P2Y_{12}$ receptor to prevent further signaling and platelet activation.

12.2 Pharmacodynamics

Cangrelor inhibits activation and aggregation of platelets. After administration of a 30 mcg/kg IV bolus followed by a 4 mcg/kg/min IV infusion, platelet inhibition occurs within 2 minutes.

Figure 2 shows the effect on platelet activity, and its relation to cangrelor plasma concentration, of administering a 30 mcg/kg IV bolus, followed by a 1-hour 4 mcg/kg/min IV infusion, of cangrelor. The anti-platelet effect is maintained for the duration of the infusion. After discontinuation of the infusion, the anti-platelet effect decreases rapidly and platelet function returns to normal within 1 hour.

Figure 2: Cangrelor PD Characteristics



12.3 Pharmacokinetics

KENGREAL administered intravenously has linear pharmacokinetics in both healthy volunteers and patients. KENGREAL is rapidly distributed and metabolized, reaching C_{max} within 2 minutes after administration of an intravenous bolus followed by infusion.

Distribution

In a study in healthy volunteers, KENGREAL administration at a dose of 30 mcg/kg bolus plus 4 mcg/kg/min showed a volume of distribution of 3.9 L. Plasma protein binding of KENGREAL is about 97-98%.

Metabolism

KENGREAL is deactivated rapidly in the circulation by dephosphorylation to its primary metabolite, a nucleoside, which has negligible anti-platelet activity. KENGREAL's metabolism is independent of hepatic function and it does not interfere with other drugs metabolized by hepatic enzymes.

Elimination

Following IV administration of [^{3}H] KENGREAL 58% of radioactivity was recovered in urine. The remaining 35% of radioactivity was in feces, presumably following biliary excretion. The average elimination half-life of KENGREAL is about 3-6 minutes.

Specific Populations

KENGREAL pharmacokinetics are not affected by sex, age, renal status or hepatic function. No dose adjustment is needed for these factors *[see Use in Specific Populations (8)]*.

Weight

Although weight was a significant covariate for PK with higher clearance in heavier patients, the impact of weight on drug exposure is accounted by the use of weight-based dosing.

Drug-Drug Interactions

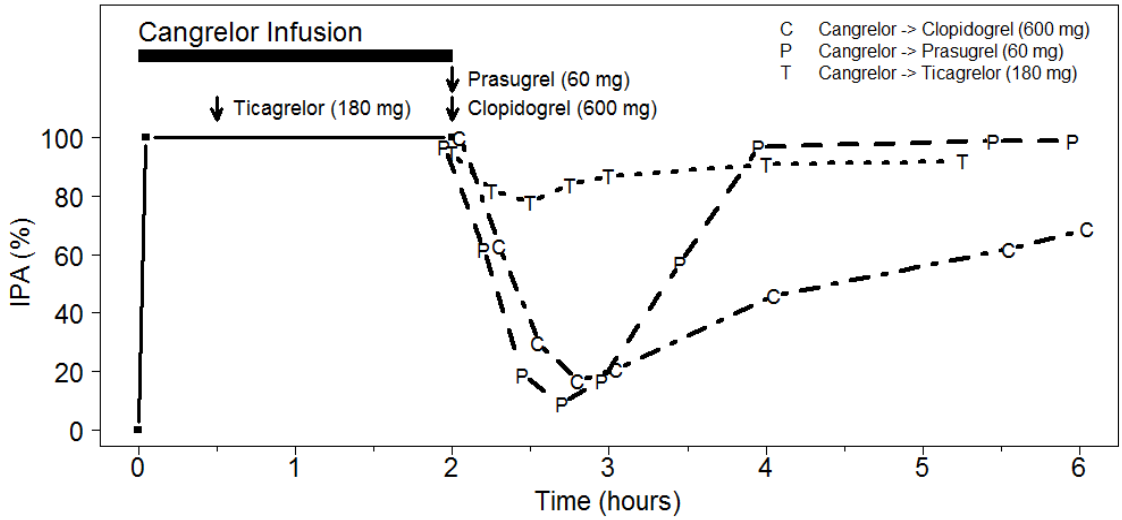
Co-administration of cangrelor with unfractionated heparin, aspirin, and nitroglycerin was formally studied in healthy subjects, with no evidence of an effect on the PK/PD of cangrelor.

In clinical trials cangrelor has been co-administered with bivalirudin, low molecular weight heparin, clopidogrel, prasugrel, and ticagrelor without clinically detectable interactions.

The expected antiplatelet effect of a 600 mg loading dose of clopidogrel or a 60 mg loading dose of prasugrel was blocked when clopidogrel or prasugrel was administered during a cangrelor infusion *[see Drug Interactions (7.1)]*.

In contrast, the antiplatelet effect of a 180 mg ticagrelor loading dose was not altered significantly when ticagrelor was administered during cangrelor infusion *[see Drug Interactions (7.1)]*.

Figure 3: Inhibition (Mean) of 20 µM ADP-induced Platelet Aggregation (IPA) Measured by Light Transmission Aggregometry after Cangrelor 30 mcg/kg Bolus and 120-minute 4 mcg/kg Infusion with Transition to Other Oral $P2Y_{12}$ Platelet Inhibitors.



As shown in Figure 3, discontinuation of cangrelor infusion, followed by administration of the irreversible $P2Y_{12}$ platelet inhibitors clopidogrel and prasugrel led to a 1-hour decrease in IPA followed by an increase in inhibition of platelet aggregation beginning at about one hour. This time course of platelet inhibition reflects the pharmacokinetics of cangrelor (offset) followed by the absorption and metabolism of clopidogrel and prasugrel to active metabolites (onset). Administration of ticagrelor, a reversible $P2Y_{12}$ platelet inhibitor, during the cangrelor infusion led to minimal decrease in platelet inhibition for approximately 0.5 hours following discontinuation of the cangrelor infusion. Administering ticagrelor during cangrelor infusion does not attenuate the anti-platelet effect of ticagrelor.

In vitro studies suggest that neither cangrelor nor its major metabolites inhibit the activity of the hepatic CYP isoenzymes at therapeutic concentrations. Therefore, cangrelor administration is not expected to interfere with the hepatic metabolism of other concomitantly administered therapeutic agents.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No carcinogenicity studies were conducted.

Mutagenesis

Cangrelor was non-mutagenic and non-clastogenic in genetic toxicology studies, including in vitro bacterial gene mutation assay, mouse lymphoma thymidine kinase assay, chromosome aberration assay in human peripheral lymphocytes, and in vivo bone marrow micronucleus assay in mice.

Impairment of Fertility

Cangrelor had no significant effect on male or female rats fertility treated for 28 days, or on early embryonic development at steady state plasma concentration (Css) of approximately the same as that achieved in the PCI setting at the MRHD.

14 CLINICAL STUDIES

14.1 CHAMPION PHOENIX Trial

The CHAMPION PHOENIX trial was intended to test whether faster platelet inhibition with cangrelor at the time of PCI would reduce the rate of periprocedural thrombotic events compared to a drug with a slower antiplatelet effect, clopidogrel, given at about the time of PCI. It was a randomized, double-blind study in which patients with coronary artery disease (stable angina, UA/NSTEMI, STEMI) requiring PCI and receiving standard therapy including aspirin and heparin or bivalirudin were randomized 1:1 to KENGREAL (n=5472) or to clopidogrel 300 or 600 mg (n=5470). Patients who had already taken an oral $P2Y_{12}$ platelet inhibitor were not eligible to enroll. Patients administered glycoprotein IIb/IIIa inhibitors (GPI) or for whom GPI use was planned were also not eligible to enroll. PHOENIX was thus a study of people undergoing PCI who had not been previously treated with anti-platelet therapy other than aspirin.

The primary outcome measure was the first occurrence of any one of the composite endpoint of all-cause mortality, myocardial infarction (MI), ischemia-driven revascularization (IDR), and stent thrombosis (ST) within 48 hours after randomization.

KENGREAL was administered as 30 mcg/kg bolus followed by 4 mcg/kg/min infusion for 2 to 4 hours. Clopidogrel 600 mg was administered immediately at the end of the KENGREAL infusion in patients randomized to KENGREAL. Clopidogrel 300 mg or 600 mg was administered shortly before PCI or shortly afterward, in patients randomized to clopidogrel.

KENGREAL significantly reduced the occurrence of primary composite endpoint events compared to clopidogrel (relative risk reduction [RRR] 22%). Most of the effect was a reduction in post-procedural MIs detected solely by elevations in CK-MB (type 4a MI). KENGREAL did not reduce the risk of death. Table 2 shows the study results for the primary composite endpoint and the contribution of each component to the primary endpoint.

Table 2: Primary Endpoint and Its Component Events at 48 Hours in CHAMPION PHOENIX (mITT population[a])

	KENGREAL (N=5470) n (%)	**Clopidogrel (N=5469)** n (%)	**KENGREAL vs. clopidogrel**	
			OR (95% CI)	p-value
Primary Endpoint Death/MI/IDR/ST	257 (4.7)	322 (5.9)	0.78 (0.66,0.93) [b]	0.005
Death	18 (0.3)	18 (0.3)		
MI	202 (3.7)	254 (4.6)		
IDR	10 (0.2)	14 (0.3)		
ST	27 (0.5)	36 (0.7)		

Note: if a subject had more than one event at 48 hours, then worst outcome counted (death >MI >IDR >ST)
[a] The mITT population is all randomized subjects who received at least one dose of study drug and underwent the index PCI procedure
[b] Based on logistic model adjusted for loading dose and baseline patient status for primary endpoint

A supplementary analysis was also performed omitting two subcomponent events of the primary endpoint that were of lesser clinical significance: intraprocedural stent thrombosis (defined as a new or increasing thrombus within or adjacent to a deployed stent occurring during the index PCI procedure), and myocardial infarction with less than a 10-fold increase in CK-MB, or with less than a 5-fold increase in CK-MB in the presence of new Q waves or new left bundle branch block (LBBB). These results are shown in Table 3.

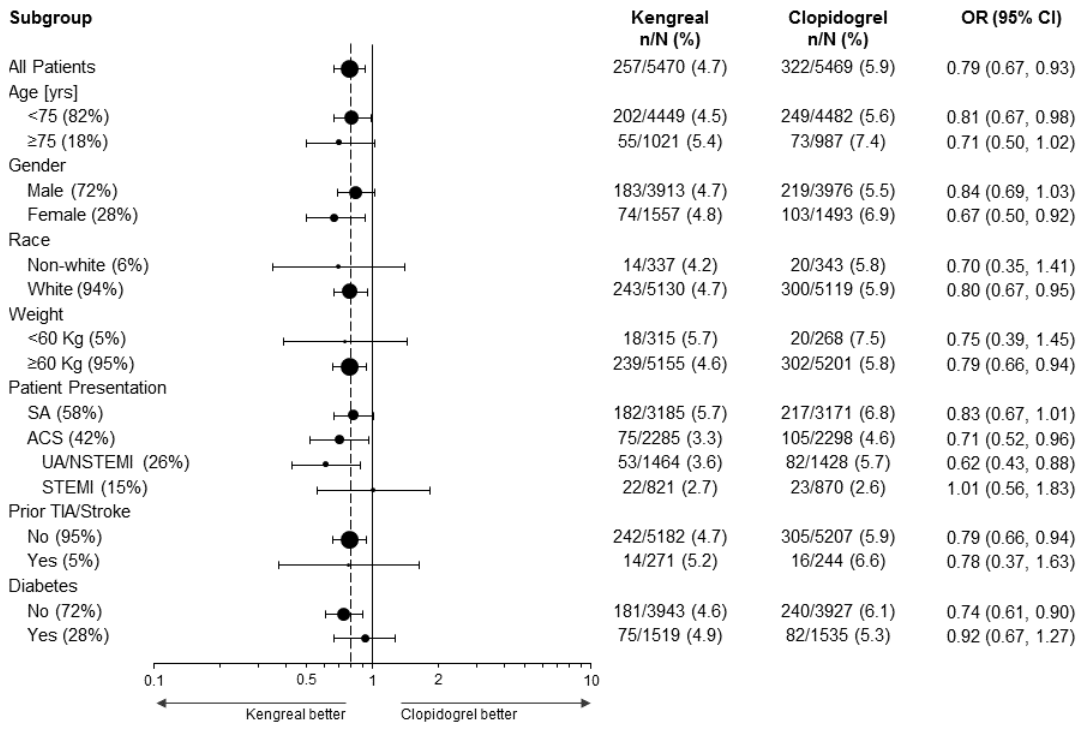
Table 3: Supplementary Endpoint and Its Component Events at 48 Hours in CHAMPION PHOENIX (mITT population)

n (%)	KENGREAL **(N=5470)**	Clopidogrel **(N=5469)**	KENGREAL vs. clopidogrel **OR (95% CI)**
Supplementary Endpoint Death/SCAI-MI/IDR/ARC-ST	79 (1.4)	114 (2.1)	0.69 (0.52,0.92)
Death	18 (0.3)	18 (0.3)	
SCAI-MI[a]	48 (0.9)	80 (1.5)	
IDR	13 (0.2)	16 (0.3)	
ARC-ST[b]	0 (0.0)	0 (0.0)	

Note: if a subject had more than one event at 48 hours, then worst outcome counted (death >SCAI-MI >IDR >ARC-ST)
[a] SCAI MI: CK-MB ≥10X ULN, or CK-MB ≥5X ULN with new Q waves or new LBBB
[b] ARC-ST defined according to the ARC definition [Cutlip et al. 2007]

The effect of KENGREAL appeared to be consistent in a variety of pre-specified and other clinically important subgroups (see Figure 4).

Figure 4: CHAMPION PHOENIX Study: Primary Efficacy Endpoint by Subgroup (mITT Population[a])



[a] The mITT population is all randomized subjects who received at least one dose of study drug and underwent the index PCI procedure.
Note: The figure above presents effects in various subgroups most of which are baseline characteristics and most of which were pre-specified (patient presentation and weight were not pre-specified subgroups). The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

14.2 CHAMPION PCI and PLATFORM Trials

Two additional concurrent clinical trials of the effect of KENGREAL in patients undergoing percutaneous coronary intervention, CHAMPION PCI and CHAMPION PLATFORM were conducted and terminated early for futility. They were completed prior to the design and conduct of CHAMPION PHOENIX. The comparative characteristics and outcomes of each trial are shown in Table 4.

Table 4: Summary of the CHAMPION Trials

		PCI	PLATFORM	PHOENIX
Subjects Randomized (% of planned enrollment)		8,846 (99%)	5,346 (84%)	11,145 (100%)
Primary Endpoint at 48 hours		Death, MI, or IDR	Death, MI, or IDR	Death, MI, IDR, or ST
Outcome of primary analysis, OR (95% CI)		1.05 (0.88, 1.24)	0.87 (0.71, 1.07)	0.78 (0.66, 0.93)
Clopidogrel dose and time in clopidogrel arm		600 mg immediately before PCI	600 mg immediately after PCI	300 or 600 mg shortly before or shortly after PCI
Population enrolled (%)	Stable angina	15%	5%	58%
	UA/NSTEMI	74%	95%	26%
	STEMI	11%	Excluded	16%

16 HOW SUPPLIED/STORAGE AND HANDLING

KENGREAL is supplied as a sterile lyophilized powder in single-use 10 mL vials.

- NDC # 10122-620-01: 10 mL vial containing 50 mg cangrelor
- NDC # 10122-620-10: 10 count of 10 mL vials containing 50 mg cangrelor

Vials of KENGREAL should be stored at USP Controlled Room Temperature, [20°C to 25°C (68°F to 77°F) with excursions between 15°C and 30°C (59°F and 86°F) permitted].

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