PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]KENGREXAL®

cangrelor

50 mg powder for solution for injection as cangrelor tetrasodium, intravenous use

Manufacturer's Standard

Platelet aggregation inhibitors excl. heparin, B01AC25

Sponsor :

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Date of Initial Authorization:
JAN 19, 2023

Submission Control Number: 255032

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

KENGREXAL (cangrelor) is indicated for reducing the risk of thrombotic cardiovascular events (periprocedural myocardial infarction (MI), repeat coronary revascularization, and stent thrombosis (ST)) in patients with coronary artery disease undergoing percutaneous coronary intervention who have not been treated with an oral $P2Y_{12}$ platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥75 years of age): No overall differences in safety or effectiveness were observed between the geriatric population and patients <75 years of age.

2 CONTRAINDICATIONS

KENGREXAL is contraindicated in:

- patients with significant active bleeding or an increased risk of bleeding (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS).
- patients who had an ischemic stroke or any previous hemorrhagic stroke.
- patients with known hypersensitivity (e.g., anaphylaxis) to KENGREXAL or any component of the product, including any non-medicinal ingredient or component of the container (see 8 ADVERSE REACTIONS). For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- KENGREXAL is intended for intravenous injection or infusion only, in an acute and hospital setting

Transitioning Patients to Oral $P2Y_{12}$ Therapy

To maintain platelet inhibition after discontinuation of KENGREXAL infusion, administer an oral $P2Y_{12}$ platelet inhibitor, as described below:

- Ticagrelor: 180 mg immediately after discontinuation of KENGREXAL (see 9 DRUG INTERACTIONS and 10 CLINICAL PHARMACOLOGY).
- Prasugrel: 60 mg immediately after discontinuation of KENGREXAL. Do not administer prasugrel prior to discontinuation of KENGREXAL (see 9 DRUG INTERACTIONS and 10 CLINICAL PHARMACOLOGY).
- Clopidogrel: 600 mg immediately after discontinuation of KENGREXAL. Do not administer clopidogrel prior to discontinuation of KENGREXAL (see 9 DRUG INTERACTIONS and 10 CLINICAL PHARMACOLOGY).

4.2 Recommended Dose and Dosage Adjustment

- The recommended dosage of KENGREXAL is a 30 µg/kg IV bolus followed immediately by a 4 µg/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. The infusion may be continued for maximal duration of 4 hours.
- No dosage adjustment is required for patients with mild, moderate, or severe renal impairment (see 10 CLINICAL PHARMACOLOGY).
- KENGREXAL has not been studied in patients with hepatic impairment. The metabolism of KENGREXAL is not dependent of hepatic function, so dosage adjustment is not expected to be required for patients with hepatic impairment (see 10 CLINICAL PHARMACOLOGY).
- **Pediatrics (<18 years of age):** Health Canada has not authorized an indication for pediatric use (see 1 INDICATIONS, 1.1 Pediatrics).
- **Geriatrics (≥75 years of age)**: No dose adjustment is needed in older patients.

4.3 Reconstitution

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

Aseptic procedures should be used for the preparation of KENGREXAL.

Preparation

Reconstitute the vial prior to dilution in a bag. For each 50 mg/vial, reconstitute by adding 5 mL of Sterile Water for Injection (see Table 1). 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, colourless to pale yellow solution. Parenteral drug products should be inspected visually for particulate matter after reconstitution.

Table 1: Reconstitution

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Concentration per mL
10 mL	5 mL Sterile Water for Injection	5 mL	10 mg/mL

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 µg/mL and should be sufficient for at least 2 hours of dosing. Patients 100 kg and over will require a minimum of two bags.

Reconstituted KENGREXAL should be diluted immediately. Diluted KENGREXAL 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.

4.4 Administration

Administer KENGREXAL in a dedicated IV line.

Administer the bolus volume rapidly (<1 minute) from the diluted bag via manual IV push or pump. Ensure bolus is completely administered before the start of PCI. Start the infusion immediately after administration of the bolus (see 4 DOSAGE AND ADMINISTRATION).

4.5 Missed Dose

Not applicable.

5 OVERDOSAGE

There is no specific treatment to reverse the antiplatelet effect of KENGREXAL but platelet function is restored within 1 hour after KENGREXAL is discontinued.

In clinical trials, 36 patients received an overdose of KENGREXAL, ranging from 36 to 300 µg/kg (bolus dose) or 4.8 to 13.7 µg/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.

Bleeding was the most frequently observed adverse event and occurred in 3 patients of the 36 who overdosed (one GUSTO moderate and 2 GUSTO mild bleedings).

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous injection	50 mg of KENGREXAL lyophilized powder in a single-use 10 mL glass vial for reconstitution	Mannitol, sodium hydroxide (for pH adjustment), sorbitol

KENGREXAL is supplied as a sterile lyophilized powder in single-use 10 mL vials containing 50 mg cangrelor.

7 WARNINGS AND PRECAUTIONS

Cardiovascular

Cardiac tamponade

Treatment with KENGREXAL may increase the risk of cardiac tamponade. In the CHAMPION program studies conducted in patients undergoing PCI, there were more cardiac tamponades at 30 days with cangrelor (0.12%) than with clopidogrel (0.02%).

Endocrine and Metabolism

Fructose intolerance

KENGREXAL contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Hematologic

Risk of bleeding

KENGREXAL increases the risk of bleeding.

In CHAMPION PHOENIX, bleeding events of all severities were more common with KENGREXAL than with clopidogrel (see 8 ADVERSE REACTIONS). Bleeding complications with KENGREXAL were consistent across a variety of clinically important subgroups (see Figure 1). In patients with severe renal impairment a higher rate of GUSTO moderate bleeding was reported in the cangrelor group (6.7%) compared to clopidogrel (1.4%).

Once KENGREXAL is discontinued, platelet function is restored after 1 hour (see 10 CLINICAL PHARMACOLOGY).

Although most bleeding associated with the use of cangrelor occurs at the site of arterial puncture, hemorrhage can occur at any site. Any unexplained fall in blood pressure or hematocrit should lead to the serious consideration of a hemorrhagic event and the cessation of cangrelor administration. Cangrelor should be used with caution in patients with disease states associated with an increased bleeding risk and in patients taking medications that may increase the risk of bleeding.

Intracranial hemorrhage

Treatment with KENGREXAL may increase the risk of intracranial hemorrhage. In the pooled safety analysis of CHAMPION program studies conducted in patients undergoing PCI, there were more intracranial bleeds at 30 days with cangrelor (0.07%) than with clopidogrel (0.02%), of which 4 bleeds with cangrelor and 1 bleed with clopidogrel were fatal. KENGREXAL is contraindicated in patients who had an ischemic stroke or any previous hemorrhagic stroke (see 2 CONTRAINDICATIONS).

Immune

Hypersensitivity

Hypersensitivity reactions may occur after treatment with KENGREXAL. A higher rate of serious cases of hypersensitivity were recorded with cangrelor (0.05%) than with control (0.02%). These included cases of anaphylactic reactions/shock, angioedema, bronchospasm (8 ADVERSE REACTIONS).

Renal

Effects on renal function

Cangrelor should be used with caution in patients with severe renal impairment. In patients with severe renal impairment (creatinine clearance 15 to 30 mL/min) a higher rate of worsening in renal function (3.2%) was reported in the cangrelor group compared to clopidogrel (1.4%). In addition, a higher rate of GUSTO moderate bleeding was reported in the cangrelor group (6.7%) compared to clopidogrel (1.4%). In the CHAMPION program studies conducted in patients undergoing PCI, events of acute renal failure (0.1%), renal failure (0.1%), and increased serum creatinine (0.2%) were reported to occur after administration of cangrelor in clinical trials (see 8 ADVERSE REACTIONS).

Reproductive Health: Female and Male Potential

Fertility

No human data on the effect of cangrelor on fertility is available. Animal studies with cangrelor demonstrate a risk of impaired male fertility at high exposure doses (12 times the maximum recommended human dose [MRHD]). Female fertility was not impacted with cangrelor treatment, however, reduced post-implantation survival of embryos was observed at dose 3 times MRHD (see 16 NON-CLINICAL TOXICOLOGY).

Respiratory

Risk of dyspnea

Treatment with cangrelor may increase the risk of dyspnea. In the CHAMPION program studies conducted in patients undergoing PCI dyspnea (including exertional dyspnea) occurred more commonly in patients treated with cangrelor (1.3%) than clopidogrel (0.4%). Most dyspnea events were mild or moderate in severity. The mean duration of dyspnea was 12.7 hours, and the median duration of dyspnea was 2 hours in patients receiving cangrelor (see 8 ADVERSE REACTIONS). In most cases dyspnea started during cangrelor infusion and ended after infusion completion.

7.1 Special Populations

7.1.1 Pregnant Women

There are no available data on cangrelor use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

In the animal studies in pregnant rabbits and rats no treatment related maternal toxicity was observed at doses approximately 3 times MRHD. However, increased incidence of intrauterine deaths is observed in animals at this dose. Exposure of cangrelor in pregnant rats and rabbits resulted in increased incidence of incomplete ossification of skull and sternebrae bone and retarded fetal development at levels those expected in humans (see 16 NON-CLINICAL TOXICOLOGY).

KENGREXAL should not be used during pregnancy unless there has been careful consideration of the benefit for the mother and the risk to the fetus (see 7 WARNINGS AND PRECAUTIONS and 16 NON-CLINICAL TOXICOLOGY).

7.1.2 Breast-feeding

There are no data on the presence of cangrelor in human milk or animal milk, the effects on the breastfed infant, or the effects on milk production. Due to its short half-life, cangrelor exposure is expected to be very low in the breastfed infant. However, risk to breastfed infant cannot be excluded.

7.1.3 Pediatrics

Pediatrics (<18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

In CHAMPION PHEONIX, 18% of patients were ≥75 years of age. No overall differences in safety or effectiveness were observed between these patients and those patients <75 years (see 14 CLINICAL TRIALS).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse reactions with cangrelor include mild and moderate bleeding and dyspnea. Serious adverse reactions associated with cangrelor in patients with coronary artery disease include severe/life threatening bleeding and hypersensitivity.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety of KENGREXAL has been evaluated in 13,301 subjects in controlled trials, of whom 5529 were in the CHAMPION PHOENIX trial.

Bleeding

There was a greater incidence of bleeding with KENGREXAL than with clopidogrel. No baseline demographic factor altered the relative risk of bleeding with KENGREXAL (see Table 3 and Figure 1).

Table 3: Major Bleeding Results in the CHAMPION PHOENIX Study (Non-CABG Related Bleeding)

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

CABG = coronary artery bypass grafting; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; TIMI = Thrombolysis in Myocardial Infarction

[a] Intracranial hemorrhage or bleeding resulting in substantial hemodynamic compromise requiring treatment.

[b] Requiring blood transfusion but not resulting in hemodynamic compromise.

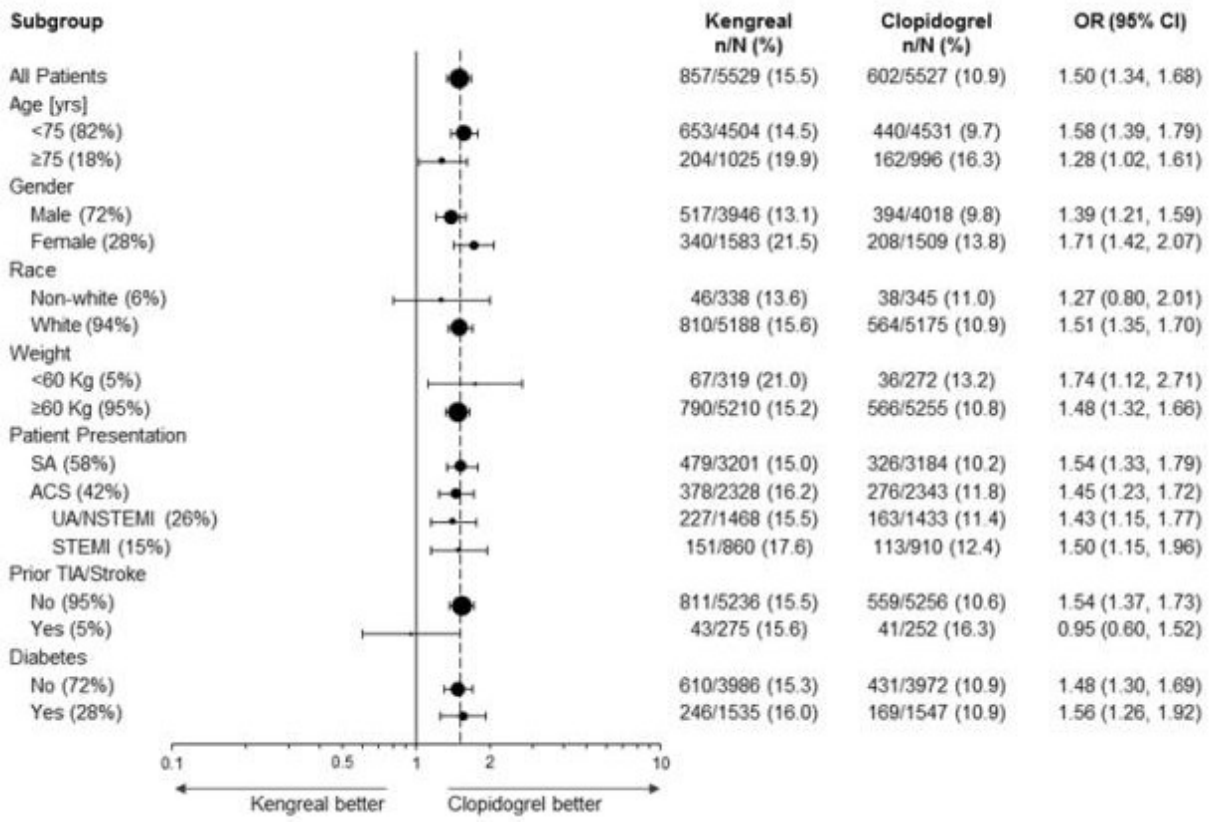
[c] All other bleeding not included in severe or moderate.

[d] 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%).

[e] 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%).

Note: Safety population is all randomized subjects who received at least one dose of study drug.

Figure 1: Bleeding Results in the CHAMPION PHOENIX Study (All Non-CABG Related)



ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CI = confidence interval; Kengreal = KENGREXAL; OR = odds ratio; SA =stable angina; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischemic attack; UA/NSTEMI = unstable angina and non-ST-segment elevation myocardial infarction

Note: 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 KENGREXAL and 0.1% for clopidogrel. Discontinuation for non-bleeding adverse events was low and similar for KENGREXAL (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 KENGREXAL.

Non-bleeding Adverse Reactions

Hypersensitivity

Serious cases of hypersensitivity were more frequent with KENGREXAL (0.05%) than with control (0.02%). These included anaphylactic reactions, anaphylactic shock, bronchospasm, angioedema, and stridor.

Decreased renal function

Worsening renal function was reported in 3.2% of KENGREXAL 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 KENGREXAL (1.3%) than with control (0.4%).

Table 4: Summary of Most Frequently Report TEAEs (≥1.0% of Patients in Either Treatment Arm) in the CHAMPION PHOENIX Study (Safety Population)

	Cangrelor n = 5529 n (%)	**Clopidogrel n = 5527 n (%)**
Gastrointestinal disorders		
Nausea	117 (2.1)	107 (1.9)
Vomiting	70 (1.3)	53 (1.0)
General disorders and administration site conditions		
Vessel puncture site pain	114 (2.1)	102 (1.8)
Musculoskeletal and connective tissue disorders		
Back pain	147 (2.7)	155 (2.8)
Nervous system disorders		
Headache	101 (1.8)	110 (2.0)
Respiratory, thoracic and mediastinal disorders		
Dyspnea	65 (1.2)	18 (0.3)
Vascular disorders		
Hypertension	112 (2.0)	93 (1.7)
Hypotension	63 (1.1)	48 (0.9)

8.3 Less Common Clinical Trial Adverse Reactions

Adverse reactions occurring at a frequency ≥0.1% and <1% in the CHAMPION PHOENIX trial included:

Cardiac disorders: bradycardia
Gastrointestinal disorders: diarrhoea, dyspepsia
General disorders and administration site conditions: malaise, pyrexia, vessel puncture site swelling
Infections and infestations: bronchitis, pneumonia, urinary tract infection
Nervous system disorders: presyncope
Skin and subcutaneous tissue disorders: pruritus, rash

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Table 5: Patients with Potentially Clinically Significant Values in Hematology Parameters in the CHAMPION PHOENIX Study (Safety Population)

	Cangrelor n = 5529 n/N (%)	Clopidogrel n = 5527 n/N (%)
Hematocrit ≤0.8×LLN	147/5161 (2.8)	119/5152 (2.3)
Hemoglobin ≤0.8×LLN	166/5148 (3.2)	109/5149 (2.1)
Platelet count ≥700 1000/mm^3	1/5250 (0.0)	0/5226 (0.0)
Platelet count ≤75 1000/mm^3	4/5250 (0.1)	5/5226 (0.1)

No differences between adults, geriatrics, and/or pediatrics can be ascertained.

Post-Market Findings

The following preferred terms related to Abnormal Laboratory Findings occurred in the post-market experience.

Table 6: Abnormal Laboratory Finding Adverse Drug Reactions from Post-market Sources

	Events[a,b] N = 625 n/N (%)	ICSRs[a,b] N = 285 n/N (%)
Acidosis	1 (0.2)	1 (0.4)
Blood loss anemia	1 (0.2)	1 (0.4)
Electrocardiogram ST segment elevation	5 (0.8)	5 (1.8)
Hematuria	1 (0.2)	1 (0.4)
Hemoglobin decreased	3 (0.5)	3 (1.1)
Hemolytic anemia	3 (0.5)	1 (0.4)
Hyperglycemia	1 (0.2)	1 (0.4)
Lactic acidosis	1 (0.2)	1 (0.4)

	Events[a,b] N = 625 n/N (%)	ICSRs[a,b] N = 285 n/N (%)
Platelet function test abnormal	1 (0.2)	1 (0.4)
Thrombocytopenia	4 (0.7)	4 (1.4)

ICSR = Individual Case Safety Report

[a] Total number of adverse events that occurred in the post-market experience is equal to 625.

[b] 642 adverse events correspond to 285 different ICSRs.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval use of KENGREXAL. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency.

Blood and lymphatic system disorders: blood loss anemia, hemolytic anemia
Cardiac disorders: acute myocardial infarction, atrioventricular block, cardiac arrest, cardiac failure, cardio-respiratory arrest, cardiogenic shock, coronary artery dissection, coronary artery thrombosis, myocardial infarction, pericardial effusion, ventricular fibrillation, ventricular tachycardia
Gastrointestinal disorders: glossodynia, pancreatitis, paraesthesia oral, retroperitoneal hematoma, tongue pigmentation
General disorders and administration site conditions: catheter site swelling, chest discomfort, chest pain, feeling abnormal, hyperthermia, infusion site extravasation, multiple organ dysfunction syndrome, pain, vascular stent thrombosis, vessel puncture site hematoma
Infections and infestations: sepsis
Injury, poisoning and procedural complications: coronary artery restenosis, fall, graft thrombosis, head injury, post procedural hematoma, subdural hematoma, traumatic hemothorax, vasoplegia syndrome
Investigations: ejection fraction decreased, electrocardiogram ST segment elevation, international normalised ratio increased, platelet function test abnormal
Metabolism and nutrition disorders: hyperglycemia
Nervous system disorders: brain edema, central nervous system lesion, cerebral hypoperfusion, cerebrovascular accident, hemorrhagic stroke, hemiparesis, intracranial aneurysm
Psychiatric disorders: anxiety, delirium, drug abuse
Renal and urinary disorders: hematuria
Respiratory, thoracic and mediastinal disorders: asphyxia, epistaxis, lung infiltration, pneumonia aspiration, pneumothorax, pulmonary edema, respiratory distress, respiratory failure
Skin and subcutaneous tissue disorders: hyperhidrosis
Vascular disorders: hematoma, shock, thrombosis

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

When clopidogrel or prasugrel are administered early during KENGREXAL infusion the expected antiplatelet effect is reduced or abolished following KENGREXAL discontinuation and until the next dose is administered. Therefore, administer clopidogrel or prasugrel only after KENGREXAL infusion is discontinued (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY).

Thienopyridines, such as clopidogrel and prasugrel, have pharmacokinetic properties distinct from cangrelor, with a longer interval between administration and $P2Y_{12}$ inhibition. Administration of clopidogrel or prasugrel immediately after cangrelor discontinuation leads to a period of 1 hour in which ADP-mediated platelet aggregation recovers to baseline values. This is followed by the progressive onset of clopidogrel- or prasugrel-mediated $P2Y_{12}$ inhibition.

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).

A pharmacodynamic interaction study has also been conducted with cangrelor and ticagrelor, a reversible $P2Y_{12}$ platelet inhibitor. The antiplatelet effect of a 180 mg ticagrelor loading dose was not altered significantly when ticagrelor was administered during cangrelor infusion.

Administration of ticagrelor during the cangrelor infusion led to a 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.

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

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.

In vitro inhibition of BCRP by the metabolite AR-C69712XX at clinically relevant concentrations has been observed. Since AR-C69712 is not a substrate for transporters that work in concert with BCRP including the OATP1B or OAT transporters, clinically relevant interaction of AR-C69712 with BCRP is unlikely. Since the possible interactions are not investigated for the *in vivo* situation, caution is advised when cangrelor is to be combined with a BCRP substrate. AR-C69712XX did not inhibit any of the other ABC or SLC transporters at clinically relevant concentrations.

9.3 Drug-Behavioural Interactions

Interactions with behavioural risks have not been established.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 7: Established or Potential Drug-Drug Interactions

Common Name	Source of Evidence	Effect	Clinical comment
BCRP substrates	T	*In vitro* inhibition of BCRP by the metabolite AR-C69712XX at clinically relevant concentrations	Caution is advised when cangrelor is to be combined with a BCRP substrate

CS = case study; CT = clinical trial; T = theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Cangrelor is a direct $P2Y_{12}$ platelet receptor inhibitor that blocks ADP binding to the receptor and consequent ADP-induced platelet activation and aggregation. Cangrelor is an ATP structural analogue that binds selectively and reversibly to the $P2Y_{12}$ receptor to prevent further signaling and platelet activation. The inhibition of ADP-induced platelet activation and aggregation during PCI reduces the risk of thrombotic cardiovascular events.

The binding of cangrelor to the $P2Y_{12}$ receptor is suspected to prevent the binding of thienopyridines active metabolites. This mechanism is believed to be responsible for the loss of expected efficacy of thienopyridines when administered during cangrelor IV infusion.

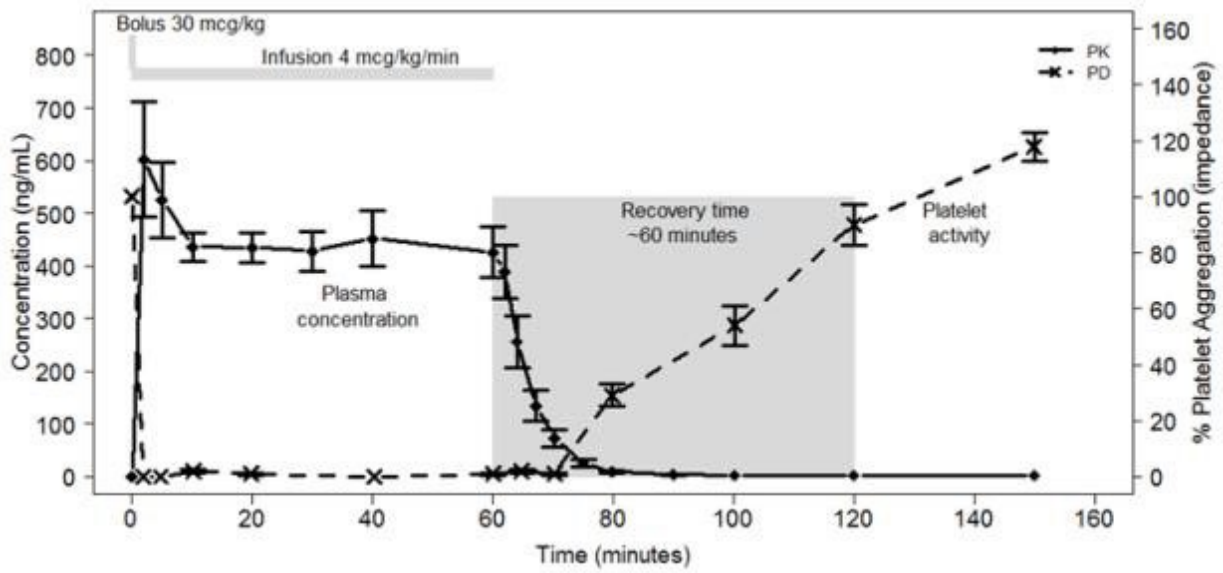
In plasma, cangrelor undergoes rapid inactivation by dephosphorylation to the major circulating metabolite, the nucleoside AR-C69712XX, which shows no pharmacological activity.

10.2 Pharmacodynamics

Cangrelor inhibits activation and aggregation of platelets. After administration of a 30 µg/kg IV bolus followed by a 4 µg/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 µg/kg IV bolus, followed by a 1-hour 4 µg/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 Pharmacodynamic Characteristics



PD = pharmacodynamics; PK = pharmacokinetics

Cardiac Electrophysiology

In a randomized, double-blind, placebo- and positive-controlled, 4-way crossover ECG study, 60 healthy subjects were treated; all receiving cangrelor at therapeutic (30 µg/kg IV bolus plus 4 µg/kg/min of IV infusion for 3 h) and supratherapeutic (60 µg/kg IV bolus plus 8 µg/kg/min IV infusion for 3 h) doses. At the doses tested, cangrelor did not prolong the QTc interval to any clinically relevant extent. At the therapeutic dose, change from baseline in mean heart rate was significantly different from placebo at 2, 30, 60, and 120 minutes post cangrelor administration. The maximum difference from placebo in mean change from baseline heart rate was 5.3 bpm at the therapeutic dose and 6.5 bpm at the supratherapeutic dose, both at 120 min post-dose. There was in increased incidence of heart rate outliers associated with cangrelor treatment. The number of subjects with heart rate > 90 bpm were 4 (7%), 8 (14%), 8 (14%), for the placebo, cangrelor therapeutic, and cangrelor supratherapeutic groups, respectively.

10.3 Pharmacokinetics

Table 8: Summary of Cangrelor Pharmacokinetic Parameters in Healthy Volunteers

	C_{max} (ng/mL)	T_{max} (min)	$t_{½}$ (min)	$AUC_{0-\infty}$ (ng·h/mL)	CL (L/h)	Vz (L)
30 µg/kg IV bolus plus 4 µg/kg/min IV infusion	665±213	3 (2-30)	3.6±1.2	488±94	43.9±8.03	3.88±1.18

$AUC_{0-\infty}$ = area under the concentration time curve extrapolated to infinity; CL = plasma clearance; C_{max} = maximum concentration; $t_{1/2}$ = half-life; T_{max} = time to maximal concentration; Vz = volume of distribution

Absorption

KENGREXAL administered IV has linear pharmacokinetics in both healthy volunteers and patients. KENGREXAL is rapidly distributed and metabolized, reaching C_{max} within 2 minutes after administration of an IV bolus followed by infusion. The bioavailability of cangrelor is complete and immediate. A steady state concentration of 488 ng/mL is rapidly reached within 10 minutes.

Distribution

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

Metabolism

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

Elimination

Following IV administration of 2 µg/kg/min [^{3}H]Kengrexal to healthy males, 58% of radioactivity was recovered in urine. The remaining 35% of radioactivity was in feces, presumably following biliary excretion. The average half-life of KENGREXAL is about 3 to 6 minutes.

Special Populations and Conditions

- **Pediatrics:** Cangrelor has not been evaluated in a pediatric population.
- **Age:** In a population pharmacokinetics analysis, KENGREXAL pharmacokinetics were not affected by age (18 to 66 years). No dose adjustment is needed.
- **Sex:** KENGREXAL pharmacokinetics are not affected by sex. No dose adjustment is needed.
- **Hepatic Insufficiency:** KENGREXAL pharmacokinetics are not affected by hepatic function. No dose adjustment is needed.
- **Renal Insufficiency:** Exposure to cangrelor was higher in patients with renal insufficiency, in comparison to healthy volunteers, following a plateau infusion of cangrelor at 4 µg/kg/min. In patients with renal insufficiency, C_{max} and AUC were 1.49- and 1.59-times higher, respectively, in renal insufficient patients. KENGREXAL pharmacokinetics are not affected by renal status. No safety concerns were identified with the increased exposure and the observed effect is not considered clinically relevant to warrant dose adjustment.
- **Obesity:** In a population pharmacokinetics analysis, weight was found to be a significant covariate affecting the PK of KENGREXAL. The impact of weight on the PK is accounted for by the use of weight-based dosing.

11 STORAGE, STABILITY AND DISPOSAL

Vials of KENGREXAL should be stored at Room Temperature (15°C to 30°C).

12 SPECIAL HANDLING INSTRUCTIONS

Following reconstitution and subsequent dilution of the powder, the storage period should not exceed 12 hours in 5% dextrose solution and 24 hours in normal saline at room temperature prior to use. Do not refrigerate.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

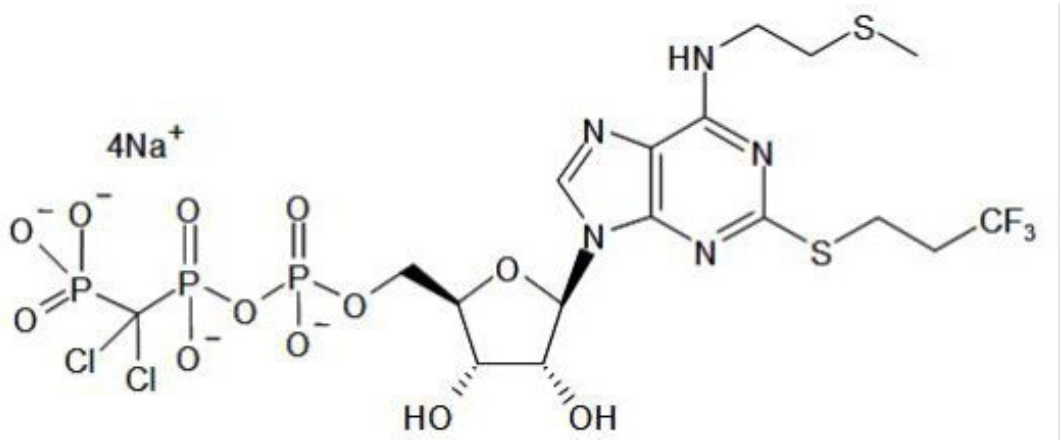
Drug Substance

Proper name: cangrelor

Chemical name: tetrasodium salt of N6-[2-(methylthio)ethyl]-2-[(3,3,3,-trifluoropropyl)-5'-adenylic acid, monanhydride with (dichloromethylene) bisphosphonic acid

Molecular formula and molecular mass: $C_{17}H_{21}N_5Cl_2F_3Na_4O_{12}P_3S_2$ and the molecular weight is 864.3 g/mol

Structural formula:



Physicochemical properties: Cangrelor for Injection is a sterile white to off-white lyophilized powder for IV infusion.

Product Characteristics:

KENGREXAL is a direct-acting $PY2_{12}$ platelet receptor inhibitor that blocks ADP-induced platelet activation and aggregation. The chemical structure is similar to adenosine triphosphate (ATP).

14 CLINICAL TRIALS

14.1 Clinical Trial by Indication

PCI

Table 9: Summary of Patient Demographics for Clinical Trials in Patients at the Time of Percutaneous Coronary Intervention

Study	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
CHAMPION PHOENIX	Randomized, double-blind, active comparator	KENGREXAL: 30 µg/kg bolus followed by 4 µg/kg/min infusion for 2-4 hours; clopidogrel 600 mg after infusion Clopidogrel: 300 mg or 600 mg shortly before or after PCI	KENGREXAL: 5472 Clopidogrel: 5470	KENGREXAL: 64.0 (56, 72) Clopidogrel: 64.0 (56, 72)	Male KENGREXAL: 3914 (71.5) Clopidogrel: 3977 (72.7) Female: KENGREXAL: 1558 (28.5) Clopidogrel: 1493 (27.3)

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, superiority study in which patients with coronary artery disease (stable angina, unstable angina and non-ST-segment elevation myocardial infarction [UA/NSTEMI], ST-segment elevation myocardial infarction [STEMI]) requiring PCI and receiving standard therapy including aspirin and heparin or bivalirudin were randomized 1:1 to KENGREXAL (n=5472) or to clopidogrel 300 or 600 mg (n=5470). The median duration of cangrelor infusion was 129 minutes. Patients who had already taken an oral $P2Y_{12}$ platelet inhibitor, patients administered glycoprotein IIb/IIIa inhibitors (GPI) or for whom GPI use was planned were not eligible to enroll. PHOENIX trial included patients 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, MI, ischemia-driven revascularization (IDR), and stent thrombosis (ST) within 48 hours after randomization.

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

KENGREXAL significantly reduced the occurrence of primary composite endpoint events compared to clopidogrel (relative risk reduction 22%). Most of the effect was a reduction in post-procedural MI detected solely by elevations in CK-MB (type 4a MI). KENGREXAL did not reduce the risk of death. Table 10 shows the study results for the primary composite endpoint and the contribution of each component to the primary endpoint.

Table 10: Primary Endpoint and its Component Events at 48 hours in CHAMPION PHOENIX (mITT Population)

	KENGREXAL (N=5470) n (%)	Clopidogrel (N=5469) n (%)	KENGREXAL 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)[a]	0.005
Death	18 (0.3)	18 (0.3)	1.00 (0.52, 1.92)[a]	>0.999
MI	207 (3.8)	255 (4.7)	0.80 (0.67, 0.97)[a]	0.022
IDR	28 (0.5)	38 (0.7)	0.74 (0.45, 1.20)[a]	0.217
ST	46 (0.8)	74 (1.4)	0.62 (0.43, 0.90)[a]	0.010

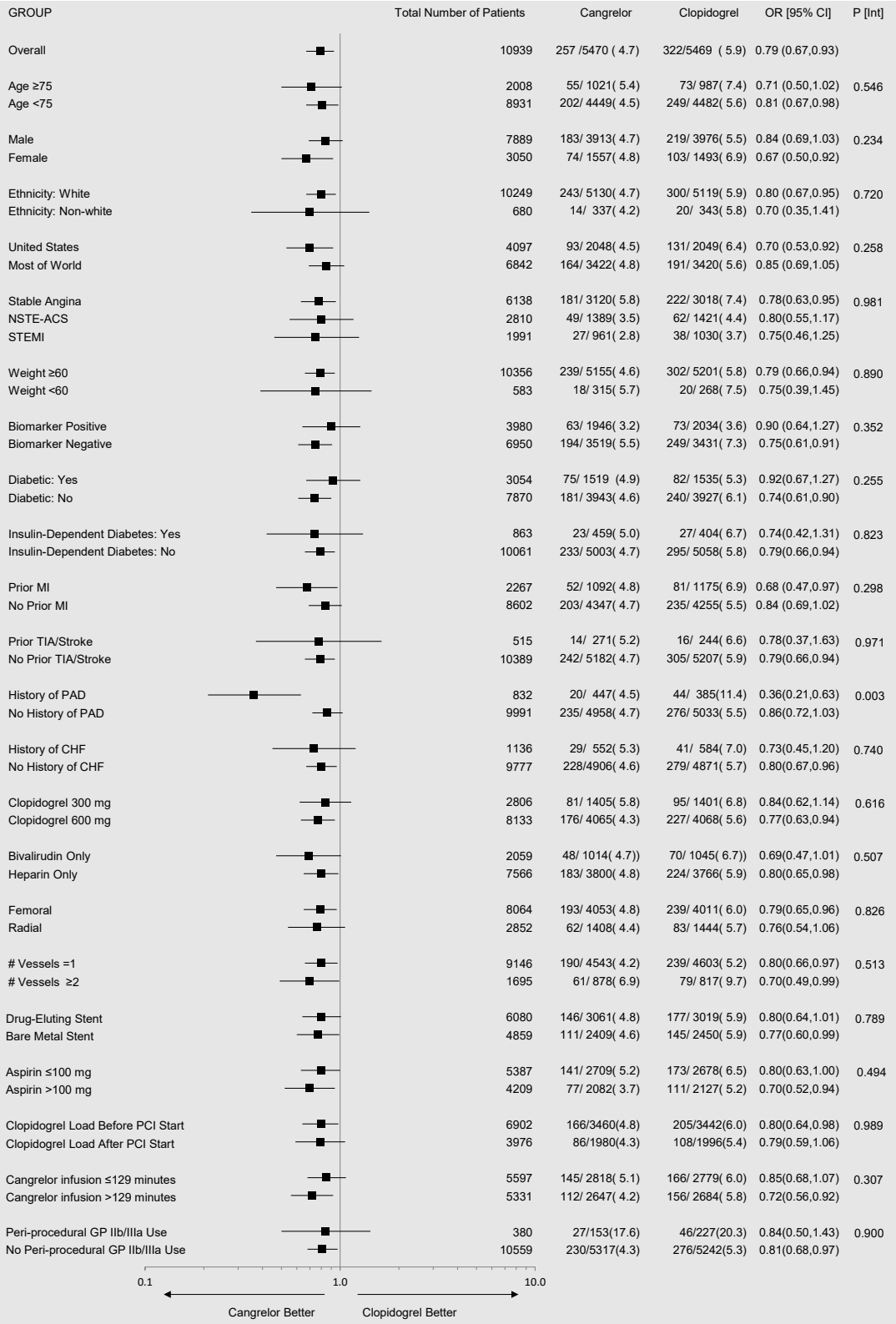
CI = confidence interval; IDR = ischemia-driven revascularization; MI = myocardial infarction; mITT = modified intent-to-treat; OR = odds ratio; PCI = percutaneous coronary intervention; ST = stent thrombosis

[a] Based on logistic model adjusted for loading dose and baseline patient status for primary endpoint

Note: The mITT population is all randomized subjects who received at least one dose of study drug and underwent the index PCI procedure.

The effect of KENGREXAL appeared to be consistent in a variety of pre-specified and other clinically important subgroups (see Figure 3).

Figure 3: CHAMPION PHOENIX Study: Primary Efficacy Endpoint by Subgroup (mITT Population)



Note: The mITT population is all randomized subjects who received at least one dose of study drug and underwent the index PCI procedure.

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 prespecified 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.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Repeat Dose Toxicity

Continuous intravenous infusion of cangrelor in rats and dogs showed evidence of toxicity in a time dependent manner. Continuous intravenous infusion of 60 µg/kg/min dose in male dogs for 7 days showed presence of inflammatory cells in urothelium epithelium, renal pelvis, ureter and urinary bladder. Continuous administration of cangrelor for 28 days demonstrated histological changes including inflammation of renal pelvis and urethra, interstitial nephritis, urothelial and tubular necrosis, tubular dilatation, distension of bladder, and urothelial hyperplasia in kidney, ureter, and urinary bladder in rats and dogs at dose of about 12 and 15 times respectively the human dose. Gastritis with ulceration, necrosis of gastric mucosa and inflammatory changes in colon and rectum were observed in male and female dogs treated with 60 µg/kg/min dose (15 times MRHD). No histological changes were observed at doses of 12 µg/kg/min (3 times human exposure) and 15 µg/kg/min (3.75 times human exposure), in rats and dogs respectively.

Dose related increase in liver enzymes, AST and ALT, were observed in both rats and dogs at dose of about 12 and 15 times respectively the human dose with no evidence of histopathological changes in liver.

While no changes in EGC parameters or heart rate were observed at any dose, an increase in the frequency of asynchronous premature ventricular contractions (PVC) was observed in one animal receiving 60 µg/kg/min dose (15 times MRHD).

Continuous infusion of cangrelor for 28 days at the dose of human exposure did not demonstrate any adverse effect in both rats and dogs.

Histological changes of renal toxicity correlated with increase in levels of plasma and urinary creatinine, as well as increased levels of urea, white blood cells, protein and glucose in urine were observed in rats and dogs as early as 3 times or 3.75 times human exposure respectively.

Carcinogenicity: No carcinogenicity studies were conducted.

Genotoxicity: 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. Cangrelor and its base metabolites are considered non-genotoxic since no gene mutations or chromosomal damage were observed in bacterial mutagenicity study.

Reproductive and Developmental Toxicology:

Cangrelor had no significant effect on male or female rat fertility treated by continuous infusion for 28 days, or on early embryonic development at steady state plasma concentration approximately the same as that achieved in the PCI setting at the MRHD. Impact on fertility in male rats including reduction in the ability to produce pregnancy in mated females, reduction in sperm count, motility and abnormal sperm morphology were observed at cangrelor dose of 12 times MRHD. Increased evidence of epididymal spermatocele formation, testes tubular epithelial atrophy and oligospermia were also noted at this dose. These effects were reversed upon dose off period of 8 weeks. Cangrelor did not impact fertility in female rats at dose of 12 times MRHD. However, a reduction in post-implantation survival of embryos were observed at this dose.

A prenatal and postnatal development study in female rats demonstrated incidence of maternal mortality in dams treated at 30 µg/kg/min cangrelor (approximately 7.5 times the MRHD) continuous infusion from Day 6 of gestation up to Day 23 post-partum. Pregnancy rates, gestation index, length of gestation, numbers of live, dead, and malformed pups, sex ratio, live birth index, and lactation of the maternal animals were unaffected. Survival, physical development, behaviour, or reproductive performance for the offsprings was not affected.

An embryo-fetal development study in rabbits administered 4, 12, or 36 µg/kg/min cangrelor continuous IV infusion from Day 6 to Day 19 post-coitum resulted in increased incidences of abortion and intrauterine losses at ≥12 µg/kg/min (3 times the MRHD). Fetal growth retardation occurred at 36 µg/kg/min (9 times the MRHD) and was characterized by decreased fetal weights, slight reduction in ossification, and a slight increase in skeletal variants. Whereas treatment with 4, 12, or 36 µg/kg/min cangrelor in pregnant rats from Day 6 to Day 17 post-coitum resulted in dose-related fetal growth retardation characterized by increased incidences of incomplete ossification and unossified hind limb metatarsals at dose levels ≥3 µg/kg/min. A dose dependent and species dependent differences in severity were observed.

Cangrelor did not produce malformations in either the rat or rabbit embryo-fetal development studies and is not considered to be a teratogen.

Special Toxicology: The antigenicity of cangrelor was investigated in animals using the active systemic anaphylaxis and passive cutaneous anaphylaxis studies. Cangrelor exhibited no indication of antigenicity in both tests.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

KENGREXAL

Cangrelor

Read this carefully before you start taking **KENGREXAL** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **KENGREXAL**.

What is KENGREXAL used for?

KENGREXAL is used:

- To reduce the risk blood clots and heart attack in patients with coronary artery disease who are receiving a procedure called a percutaneous coronary intervention.
- In patients who have not been treated with certain other anti-platelet medicines.

How does KENGREXAL work?

KENGREXAL is an anti-platelet medicine. Platelets are small blood cells that help blood clot. KENGREXAL diminishes the clumping of platelets and reduces the chance of a blood clot forming.

What are the ingredients in KENGREXAL?

Medicinal ingredients: cangrelor tetrasodium.

Non-medicinal ingredients: mannitol, sodium hydroxide for pH adjustment and sorbitol.

KENGREXAL comes in the following dosage forms:

As a powder for solution for injection containing 50 mg cangrelor (as cangrelor tetrasodium).

Do not use KENGREXAL if:

- you are allergic to cangrelor or to any of the other ingredients in KENGREXAL.
- you are currently bleeding or if you have an increased risk of bleeding such as with certain medical conditions.
- you have ever had a stroke.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take KENGREXAL. Talk about any health conditions or problems you may have, including if you:

- Are or you think you may be or have been told that you are at an increased risk of bleeding. For example, some diseases and medicines may increase your risk of bleeding.
- Are taking other medicines that increase your risk of bleeding including blood thinners such as warfarin.
- Have kidney problems.
- Have been told by your doctor that you have an intolerance to some sugars.
- Are less than 18 years old.

Other warnings you should know about:

Pregnancy:

KENGREXAL should not be used during pregnancy unless necessary. This is because it is not known how it might affect an unborn baby. Before you are given this medicine, tell your healthcare professional if you are pregnant, think you may be pregnant or are planning to become pregnant. You and your healthcare professional will decide if you will be given KENGREXAL.

Breastfeeding:

Tell your healthcare professional if you are breastfeeding or planning to breastfeed. It is not known if KENGREXAL passes into breastmilk. Ask your healthcare professional for advice before breastfeeding your baby.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with KENGREXAL:

- Clopidogrel, an anti-platelet medicine used to prevent heart attack and stroke.
- Prasugrel, an anti-platelet medicine used to prevent heart attack and stroke.

How to take KENGREXAL:

- KENGREXAL will be given to you in the hospital by a healthcare professional.
- It will be injected and then infused directly into your vein.
- You may receive other anti-platelet medicines after you receive KENGREXAL.
- Follow all instructions given to you by your healthcare professional.

Usual dose:

The dose you receive will depend on your weight. The recommended dose is:

- 30 micrograms per kilogram body weight by injection, followed immediately by
- 4 micrograms per kilogram body weight per minute by infusion, for at least 2 hours. Your healthcare professional will decide if you need to be treated for longer periods.

Overdose:

KENGREXAL will be given to you by a healthcare professional. They will decide how to treat you, including stopping the treatment and monitoring for signs of side effects.

If you think you, or a person you are caring for, have taken too much KENGREXAL, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using KENGREXAL?

These are not all the possible side effects you may have when taking KENGREXAL. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Minor bruising including small red bruises on the skin or at the site of an injection under the skin causing swelling
- Nausea
- Vomiting
- Pain at the injection site
- Back pain
- Headache

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Bleeding from anywhere in the body			✓
Kidney problems: change in frequency of urination, pain when you urinate, nausea, vomiting, swelling of extremities, fatigue.		✓	
Shortness of breath		✓	
Change in blood pressure: dizziness, headaches, vision problems, shortness of breath.		✓	
UNCOMMON			
Cardiac tamponade (extra fluid or blood in sac around your heart): anxiety, restlessness, sharp pain in chest felt in the neck, shoulder, back, or abdomen, chest pain that gets worse with deep breathing or coughing, problems breathing, feeling light-headed, discomfort.			✓
Kidney failure: decrease in amount of urine, fluid retention, shortness of breath, fatigue, confusion, nausea, weakness, irregular heartbeat.			✓
Slow heart rate: chest pain, confusion or memory problems, dizziness or light-headedness, easily tiring, fatigue, fainting or near-fainting.		✓	
Presyncope (feeling like you're going to faint): dizziness or light-headedness, nauseated, trouble hearing, feel weak.		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Allergic reaction: rash, itching, throat tightening/swelling, swelling of the tongue or lips, difficulty breathing. **Severe allergic reaction:** feeling lightheaded or faint, breathing difficulties, shallow breathing, wheezing fast heartbeat, clammy skin, confusion, anxiety, collapsing, losing consciousness, sudden feeling of weakness.			✓
Intracranial hemorrhage (bleeding in the brain): headache, vomiting, drowsiness and progressive loss of consciousness, dizziness, confusion, unequal pupil size, slurred speech, loss of movement or paralysis.			✓
Angioedema (swelling of tissue under the skin): difficulty breathing; swollen face, hands and feet, genitals tongue, throat; Swelling of the digestive tract causing diarrhea, nausea or vomiting.		✓	
Sudden tightening of your airways: chest tightening, shortness of breath, wheezing, coughing, tiredness, dizziness.			✓
Coronary artery dissection (tear in a blood vessel in the heart): chest pain, rapid heartbeat or fluttery feeling in the chest, pain in the arms, shoulders, back or jaw, shortness of breath, unusual extreme tiredness, nausea, dizziness.			✓
Coronary artery perforation (hole in the artery that supplies blood to the heart): shortness of breath,			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
low blood pressure, fast heartbeat, chest pain.			
Noisy breathing that occurs due to a narrowed airway		✓	
Blood loss anemia (loss of red blood cells due to bleeding): fatigue, weakness, pale or yellowish skin, irregular heartbeat, shortness of breath, dizziness or light-headedness, chest pain, cold hands and feet.		✓	
Hemolytic anemia (destruction of red blood cells faster than they can be made): abnormal paleness or lack of color of the skin, yellowish skin, eyes and mouth, dark-coloured urine, fever, weakness, dizziness, confusion.		✓	
UNKNOWN			
High blood sugar: increased thirst and a dry mouth, frequent urination, tiredness, blurred vision, unintentional weight loss, recurrent infections.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

KENGREXAL should be stored at Room Temperature (15°C to 30°C).

Keep out of reach and sight of children.

If you want more information about KENGREXAL:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the importer Methapharm Inc., by calling +1-800-287-7686 ext. 7804.

This leaflet was prepared by Chiesi Farmaceutici S.p.A., Parma, Italy.

Last Revised JAN 19, 2023