ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Kengrexal 50 mg powder for concentrate for solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains cangrelor tetrasodium corresponding to 50 mg cangrelor. After reconstitution 1 mL of concentrate contains 10 mg cangrelor. After dilution 1 mL of solution contains 200 micrograms cangrelor.

Excipient with known effect
Each vial contains 52.2 mg sorbitol.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for injection/infusion.
White to off-white lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kengrexal, co-administered with acetylsalicylic acid (ASA), is indicated for the reduction of thrombotic cardiovascular events in adult patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) who have not received an oral P2Y12 inhibitor prior to the PCI procedure and in whom oral therapy with P2Y12 inhibitors is not feasible or desirable.

4.2 Posology and method of administration

Kengrexal should be administered by a physician experienced in either acute coronary care or in coronary intervention procedures and is intended for specialised use in an acute and hospital setting.

Posology

The recommended dose of Kengrexal for patients undergoing PCI is a 30 micrograms/kg intravenous bolus followed immediately by 4 micrograms/kg/min intravenous infusion. The bolus and infusion should be initiated prior to the procedure and continued for at least two hours or for the duration of the procedure, whichever is longer. At the discretion of the physician, the infusion may be continued for a total duration of four hours, see section 5.1.

Patients should be transitioned to oral P2Y12 therapy for chronic treatment. For transition, a loading dose of oral P2Y12 therapy (clopidogrel, ticagrelor or prasugrel) should be administered immediately following discontinuation of cangrelor infusion. Alternatively, a loading dose of ticagrelor or prasugrel, but not clopidogrel, may be administered up to 30 minutes before the end of the infusion, see section 4.5.

Use with other anticoagulant agents
In patients undergoing PCI, standard procedural adjunctive therapy should be implemented (see section 5.1).

Elderly
No dose adjustment is needed in elderly (≥75 years) patients.

Renal impairment
No dose adjustment is needed in patients with mild, moderate or severe renal insufficiency (see sections 4.4 and 5.2).

Hepatic impairment
No dose adjustment is needed (see section 5.2).

Paediatric population
The safety and efficacy of cangrelor in children aged less than 18 years has not yet been established. Currently available data are described in section 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration

Kengrexal is intended for intravenous use, only after reconstitution and dilution.

Kengrexal should be administered via an intravenous line. The bolus volume should be administered rapidly (<1 minute), from the diluted bag via manual intravenous push or pump. Ensure the bolus is completely administered before the start of PCI. Start the infusion immediately after administration of the bolus.

For instructions on reconstitution and dilution of the medicinal product before administration see section 6.6.

4.3 Contraindications

- Active bleeding or increased risk of bleeding, because of impaired haemostasis and/or irreversible coagulation disorders or due to recent major surgery/trauma or uncontrolled severe hypertension.
- Any history of stroke or transient ischaemic attack (TIA).
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Risk of bleeding

Treatment with Kengrexal may increase the risk of bleeding.

In pivotal studies conducted in patients undergoing PCI, GUSTO (Global Use of Strategies to Open Occluded Arteries), moderate and mild bleeding events were more common in patients treated with cangrelor than in patients treated with clopidogrel, see section 4.8.

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

Cangrelor has a half-life of three to six minutes. Platelet function is restored within 60 minutes of stopping infusion.

Intracranial haemorrhage

Treatment with Kengrexal may increase the risk of intracranial haemorrhage. In pivotal 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. Cangrelor is contraindicated in patients with any history of stroke/TIA, (see sections 4.3 and 4.8).

Cardiac tamponade

Treatment with Kengrexal may increase the risk of cardiac tamponade. In pivotal studies conducted in patients undergoing PCI, there were more cardiac tamponades at 30 days with cangrelor (0.12%) than with clopidogrel (0.02%), (see section 4.8).

Effects on renal function

In pivotal 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 section 4.8). In patients with severe renal impairment (creatinine clearance 15-30 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%). Cangrelor should be used with caution in these patients.

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 (0.007%). These included cases of anaphylactic reactions/shock and angioedema (see section 4.8).

Risk of dyspnoea

Treatment with Kengrexal may increase the risk of dyspnoea. In pivotal studies conducted in patients undergoing PCI dyspnoea (including exertional dyspnoea) occurred more commonly in patients treated with cangrelor (1.3%) than clopidogrel (0.4%). Most dyspnoea events were mild or moderate in severity and the median duration of dyspnoea was two hours in patients receiving cangrelor (see section 4.8).

Fructose intolerance

This medicinal product contains 52.2 mg sorbitol in each vial. Patients with hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Oral P2Y12 agents (clopidogrel, prasugrel, ticagrelor)

When clopidogrel is administered during infusion of cangrelor, the expected inhibitory effect of clopidogrel on platelets is not achieved. Administration of 600 mg clopidogrel immediately after the cessation of the cangrelor infusion results in the anticipated full pharmacodynamic effect. No clinically relevant interruption of P2Y12 inhibition was observed in phase III studies when 600 mg clopidogrel was administered immediately after discontinuation of the cangrelor infusion.

A pharmacodynamic interaction study has been conducted with cangrelor and prasugrel, which demonstrated that cangrelor and prasugrel can be administered concomitantly. Patients can be transitioned from cangrelor to prasugrel when prasugrel is administered immediately following discontinuation of the cangrelor infusion or up to one hour before, optimally at 30 minutes before the end of the cangrelor infusion to limit recovery of platelet reactivity.

A pharmacodynamic interaction study has also been conducted with cangrelor and ticagrelor. No interaction on cangrelor was observed. Patients can be transitioned from cangrelor to ticagrelor without interruption of antiplatelet effect.

Pharmacodynamic effects

Cangrelor exhibits inhibition of activation and aggregation of platelets as shown by aggregometry (light transmission and impedance), point-of care assays, such as the VerifyNow P2Y12 test, VASP-P and flow cytometry.

Following the administration of a 30 micrograms/kg bolus followed by a 4 micrograms/kg/min infusion (the PCI dose), platelet inhibition is observed within two minutes. The pharmacokinetic/pharmacodynamic (PK/PD) effect of cangrelor is maintained consistently for the duration of the infusion.

Irrespective of dose, following cessation of the infusion, cangrelor blood levels decrease rapidly and platelet function returns to normal within one hour.

Acetylsalicylic acid, heparin, nitrogycerin

No pharmacokinetic or pharmacodynamic interaction with cangrelor was observed in an interaction study with aspirin, heparin, or nitroglycerin.

Bivalirudin, low molecular weight heparin, fondaparinux, and GP IIb/IIIa inhibitors

In clinical studies, cangrelor has been co-administered with bivalirudin, low molecular weight heparin, fondaparinux, and GP IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban) with no apparent effect upon the pharmacokinetics or pharmacodynamics of cangrelor.

Cytochrome P450 (CYP)

Metabolism of cangrelor is not dependent on CYPs and CYP isoenzymes are not inhibited by therapeutic concentrations of cangrelor or its major metabolites.

Breast cancer resistance protein (BCRP)

In vitro inhibition of BCRP by the metabolite ARC-69712XX at clinically relevant concentrations has been observed. Possible implications for the *in vivo* situation have not been investigated, but caution is advised when cangrelor is to be combined with a BCRP substrate.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of Kengrexal in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Kengrexal is not recommended during pregnancy.

Breast-feeding

It is unknown whether Kengrexal is excreted in human milk. A risk to the newborns/infants cannot be excluded.

Fertility

No effect on female fertility parameters were observed in animal studies of Kengrexal. A reversible effect on fertility was observed in male rats treated with Kengrexal (see section 5.3).

4.7 Effects on ability to drive and use machines

Kengrexal has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

Table 1 depicts adverse reactions that have been identified based upon a pooling of combined data from all CHAMPION studies. Adverse reactions are classified according to frequency and system organ class. Frequency categories are defined according to the following conventions: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Table 1: Adverse reactions for cangrelor in CHAMPION pooled studies within 48 hours

System organ class	Common	Uncommon	Rare	Very rare
Infections and infestations				Haematoma infection
Neoplasms benign, malignant and unspecified (includes cysts and polyps)				Skin neoplasm bleeding
Blood and lymphatic system disorders			Anaemia, thrombo-cytopenia	
Immune system disorders			Anaphylactic reaction (anaphylactic shock), hypersensitivity	
Nervous system disorders			Haemorrhage intracranial [d] *	
Eye disorders			Eye haemorrhage	
Ear and labyrinth disorders				Ear haemorrhage
Cardiac disorders		Cardiac tamponade (pericardial haemorrhage)		

System organ class	Common	Uncommon	Rare	Very rare
Vascular disorders	Haematoma <5 cm, haemorrhage	Haemodynamic instability	Wound haemorrhage, vascular pseudoaneurysm	
Respiratory, thoracic and mediastinal disorders	Dyspnoea (dyspnoea exertional)	Epistaxis, haemoptysis	Pulmonary haemorrhage	
Gastrointestinal disorders		Retroperitoneal haemorrhage,* peritoneal haematoma, gastrointestinal haemorrhage [a]		
Skin and subcutaneous tissue disorders	Ecchymosis (petechiae, purpura)	Rash, pruritus, urticaria [f]	Angioedema	
Renal and urinary disorders		Haemorrhage urinary tract, [e] acute renal failure (renal failure)		
Reproductive system and breast disorders			Pelvic haemorrhage	Menorrhagia, penile haemorrhage
General disorders and administration site conditions	Vessel puncture site discharge	Vessel puncture site haematoma [b]		
Investigations	Haematocrit decreased, haemoglobin decreased**	Blood creatinine increased	Platelet count decreased, red blood cell count decreased, international normalised ratio increased [c]	
Injury, poisoning and procedural complications	Haematoma ≥5 cm		Contusion	Periorbital haematoma, subcutaneous haematoma

Multiple related adverse reaction terms have been grouped together in the table and include medical terms as described below:

a. Upper gastrointestinal haemorrhage, mouth haemorrhage, gingival bleeding, oesophageal haemorrhage, duodenal ulcer haemorrhage, haematemesis, lower gastrointestinal haemorrhage, rectal haemorrhage, haemorrhoidal haemorrhage, haematochezia.
b. Application site bleeding, catheter site haemorrhage or haematoma, infusion site haemorrhage or haematoma.
c. Coagulation time abnormal, prothrombin time prolonged.
d. Cerebral haemorrhage, cerebrovascular accident.
e. Haematuria, blood urine present, urethral haemorrhage.
f. Erythema, rash erythematous, rash pruritic.

* Including events with fatal outcome.

** Transfusion was uncommon 101/12,565 (0.8%).

Description of selected adverse reactions

The GUSTO bleeding scale was measured in the CHAMPION (PHOENIX, PLATFORM, and PCI) clinical trials. An analysis of non-coronary artery bypass grafting (CABG)-related bleeding is presented in Table 2.

When administered in the PCI setting, cangrelor was associated with a greater incidence of GUSTO mild bleeding compared with clopidogrel. Further analysis of GUSTO mild bleeding revealed that a large proportion of mild bleeding events were ecchymosis, oozing and <5 cm haematoma. Transfusion and GUSTO severe/life-threatening bleeding rates were similar. In the pooled safety population from the CHAMPION trials, the incidence of fatal bleeding within 30 days of dosing was low and similar in patients who received cangrelor compared to clopidogrel (8 [0.1%] vs. 9 [0.1%]).

No baseline demographic factor altered the relative risk of bleeding with cangrelor.

Table 2: Non-CABG-related bleeding

GUSTO bleeding, n (%)		
CHAMPION pooled	**Cangrelor (N=12,565)**	**Clopidogrel (N=12,542)**
Any GUSTO bleeding	2,196 (17.5)	1,696 (13.5)
Severe/life-threatening	28 (0.2)	23 (0.2)
Moderate	76 (0.6)	56 (0.4)
Mild [a]	2,109 (16.8)	1,627 (13.0)
Mild w/o ecchymosis, oozing and haematoma <5 cm	707 (5.6)	515 (4.1)
Patients with any transfusion	90 (0.7)	70 (0.6)
CHAMPION PHOENIX	**Cangrelor (N=5,529)**	**Clopidogrel (N=5,527)**
Any GUSTO bleeding	178 (3.2)	107 (1.9)
Severe/life-threatening	9 (0.2)	6 (0.1)
Moderate	22 (0.4)	13 (0.2)
Mild [b]	150 (2.7)	88 (1.6)
Mild w/o ecchymosis, oozing and haematoma <5 cm	98 (1.8)	51 (0.9)
Patients with any transfusion	25 (0.5)	16 (0.3)

CABG: Coronary Artery Bypass Graft Surgery; GUSTO: Global Use of Strategies to Open Coronary Arteries; w/o: without

[a] In the CHAMPION pooled analysis, GUSTO Mild was defined as other bleed not requiring blood transfusion or causing haemodynamic compromise.

[b] In CHAMPION PHOENIX, GUSTO Mild was defined as other bleeding requiring intervention but not requiring blood transfusion or causing haemodynamic compromise.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In clinical studies, healthy volunteers received up to two times the proposed daily dose. In clinical trials, the maximum accidental overdose was 10 times (bolus) or 3.5 times the infusion dose normally administered and bleeding was the most frequently observed adverse event.

Bleeding is the most likely pharmacological effect of overdose. If bleeding occurs appropriate supportive measures should be taken, which may include stopping the medicinal product so platelet function can return.

There is no antidote to Kengrexal, however, the pharmacokinetic half-life of Kengrexal is three to six minutes. Platelet function is restored within 60 minutes of stopping the infusion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Platelet aggregation inhibitors excluding heparin, ATC code: B01AC25.

Mechanism of action

Kengrexal contains cangrelor, a direct P2Y12 platelet receptor antagonist that blocks adenosine diphosphate (ADP)-induced platelet activation and aggregation *in vitro* and *ex vivo*. Cangrelor binds selectively and reversibly to the P2Y12 receptor to prevent further signalling and platelet activation.

Pharmacodynamic effects

Cangrelor exhibits inhibition of activation and aggregation of platelets as shown by aggregometry (light transmission and impedance), point-of care assays, such as the VerifyNow P2Y12test, VASP-P and flow cytometry. Onset of P2Y12 inhibition occurs rapidly upon cangrelor administration.

Following the administration of a 30 microgram/kg bolus followed by a 4 microgram/kg/min infusion, platelet inhibition is observed within two minutes. The pharmacokinetic/pharmacodynamic (PK/PD) effect of cangrelor is maintained consistently for the duration of the infusion.

Irrespective of dose, following cessation of the infusion, blood levels decrease rapidly and platelet function returns to normal within one hour.

Clinical efficacy and safety

The primary clinical evidence for the efficacy of cangrelor is derived from CHAMPION PHOENIX, a randomised, double-blind study comparing cangrelor (n=5,472) to clopidogrel (n=5,470), both given in combination with aspirin and other standard therapy, including unfractionated heparin (78%), bivalirudin (23%), LMWH (14%) or fondaparinux (2.7%). The median duration of cangrelor infusion was 129 minutes. GP IIb/IIIa inhibitors were permitted for bailout use only and were used in 2.9% of patients. Patients with coronary atherosclerosis were included who required PCI for stable angina (58%), non-ST-segment elevation acute coronary syndrome (NSTE-ACS) (26%), or ST-elevation myocardial infraction (STEMI) (16%).

Data from the CHAMPION pooled population of over 25,000 PCI patients provide additional clinical support for safety.

In CHAMPION PHOENIX, cangrelor significantly reduced (relative risk reduction 22%; absolute risk reduction 1.2%) the primary composite endpoint of all-cause mortality, MI, IDR, and ST compared to clopidogrel at 48 hours (Table 3).

Table 3: Thrombotic events at 48 hours in CHAMPION PHOENIX (mITT population)

		Cangrelor vs. Clopidogrel		
n (%)	**Cangrelor N=5,470**	**Clopidogrel N=5,469**	**OR (95% CI)**	**p-value**
Primary Endpoint Death/MI/IDR/ST [a]	257 (4.7)	322 (5.9)	0.78 (0.66,0.93)	0.005
Key Secondary Endpoint				
Stent thrombosis	46 (0.8)	74 (1.4)	0.62 (0.43, 0.90)	0.010
Death	18 (0.3)	18 (0.3)	1.00 (0.52, 1.92)	>0.999
MI	207 (3.8)	255 (4.7)	0.80 (0.67, 0.97)	0.022
IDR	28 (0.5)	38 (0.7)	0.74 (0.45, 1.20)	0.217

[a] Primary endpoint from logistic regression adjusted for loading dose and patient status. p-values for secondary endpoints based on Chi-squared test.
OR = odds ratio; CI = confidence interval; IDR = ischaemia-driven revascularisation; MI = myocardial infarction; mITT = modified intent-to-treat; ST = stent thrombosis.

Significant reductions in death/MI/IDR/ST and ST observed in the cangrelor group at 48 hours were maintained at 30 days (Table 4).

Table 4: Thrombotic events at 30 days in CHAMPION PHOENIX (mITT population)

		Cangrelor vs. Clopidogrel		
n (%)	**Cangrelor N=5,462**	**Clopidogrel N=5,457**	**OR (95% CI)**	**p-value [a]**
Primary Endpoint Death/MI/IDR/ST	326 (6.0)	380 (7.0)	0.85 (0.73, 0.99)	0.035
Key Secondary Endpoint				
Stent thrombosis	71 (1.3)	104 (1.9)	0.68 (0.50, 0.92)	0.012
Death	60 (1.1)	55 (1.0)	1.09 (0.76, 1.58)	0.643
MI	225 (4.1)	272 (5.0)	0.82 (0.68, 0.98)	0.030
IDR	56 (1.0)	66 (1.2)	0.85 (0.59, 1.21)	0.360

[a] p-values based on Chi-squared test.
OR = odds ratio; CI = confidence interval; IDR = ischaemia-driven revascularisation; MI = myocardial infarction; mITT = modified intent-to-treat; ST = stent thrombosis.

Paediatric Population

The European Medicines Agency has deferred the obligation to submit the results of studies with Kengrexal in one or more subsets of the paediatric population in the prevention of non-site specific embolism and thrombosis, for the treatment of thrombosis in paediatric patients undergoing diagnostic and / or therapeutic percutaneous vascular procedures. See section 4.2 for information on paediatric use.

In a prospective, open-label, single-arm, multi-center, Phase I study, cangrelor was evaluated at 2 dose levels of 0.5 and 0.25 micrograms/kg/min in 15 neonates ≤28 days of life with congenital heart disease requiring palliation with a systemic-to-pulmonary artery shunt, a right ventricle-to-pulmonary artery shunt, or a ductus arteriosus stent (see section 4.2). Platelet aggregation inhibition was assessed by light transmission aggregometry (LTA) in response to stimulation with 20 and 5 μM ADP. The % inhibition of maximal aggregation 45 minutes into cangrelor infusion and the number of subjects who achieved >90% of maximal platelet aggregation inhibition are summarized in the table below.

	Cangrelor 0.5 mcg/kg/min N=8		Cangrelor 0.25 mcg/kg/min N=7	
LTA method	using ADP 20 µM	using ADP 5 µM	using ADP 20 µM	using ADP 5 µM
N	6	5	7	5
% inhibition of maximal aggregation 45 minutes into the infusion, mean (SD) median (min; max)	89.0 (11.42) 91.2 (69.0; 100.0)	93.7 (6.45) 92.9 (84.8; 100.0)	76.3 (16.89) 69.6 (53.2; 98.3)	88.2 (13.49) 96.0 (68.1; 100.0)
Subjects who achieved >90% of maximal platelet aggregation inhibition, n (%)	3 (50)	4 (80)	2 (28.6)	3 (60)

5.2 Pharmacokinetic properties

Absorption

The bioavailability of cangrelor is complete and immediate. Cangrelor is rapidly distributed reaching C_{max} within two minutes after administration of an intravenous bolus followed by infusion. The mean steady state concentration of cangrelor during a constant intravenous infusion of 4 micrograms/kg/min is 488 ng/mL.

Distribution

Cangrelor has a volume of distribution of 3.9 L. Cangrelor is 97-98% plasma-protein bound.

Biotransformation

Cangrelor is deactivated rapidly in the plasma by dephosphorylation to form its primary metabolite, a nucleoside. The metabolism of cangrelor is independent of organ function and does not interfere with other drugs metabolised by hepatic enzymes.

Elimination

The half-life of Kengrexal is three to six minutes, independent of dose. Following the intravenous administration of a 2 micrograms/kg/min infusion of [^{3}H] cangrelor to healthy male volunteers, 93% of total radioactivity was recovered. Of the recovered material, 58% was found in urine and the remaining 35% was found in faeces, presumably following biliary excretion. Initial excretion was rapid, such that approximately 50% of the administered radioactivity was recovered in the first 24 hours, and 75% was recovered by 48 hours. Mean clearance was approximately 43.2 L/kg.

Linearity/non-linearity

The pharmacokinetic properties of cangrelor have been evaluated and found to be linear in patients and healthy volunteers.

Pharmacokinetic/pharmacodynamic relationship(s)

Special populations
The pharmacokinetics of cangrelor are not affected by gender, age, or renal or hepatic status. No dose adjustment is needed for these populations.

Paediatric population
Cangrelor infusion has been evaluated in neonatal patients (age from birth to 28 days) at a dose level of 0.25 and 0.5 micrograms/kg/min. The maximum concentrations were 19 ng/mL and 60 ng/mL, respectively, and were observed approximately 45 minutes following start of infusion. In neonates, cangrelor is rapidly metabolised into its primary metabolite AR-C69712XX. Very low or non-detectable levels of cangrelor were found 5-10 minutes post-infusion and relatively high levels of the primary metabolite were detected.

5.3 Preclinical safety data

Non-clinical data reveal no special safety risk for humans based on studies of safety pharmacology, mutagenicity and clastogenic potential.

Carcinogenicity studies have not been performed.

The primary adverse effects of cangrelor in rats and dogs occurred in the upper urinary tract and consisted of injury to renal tubules, renal pelvis, and ureter. Anatomical changes correlated with increased plasma creatinine and urea, and increased albumin and blood cells in urine. Injury to the urinary tract was reversible following cessation of dosing in an investigative study in rats.

Reproductive toxicity

Cangrelor produced dose-related foetal growth retardation characterised by increased incidences of incomplete ossification and unossified hind limb metatarsals in rats. In rabbits, cangrelor was associated with increased incidences of abortion and intrauterine losses, as well as foetal growth retardation at higher doses which may have been secondary to maternal toxicity. Cangrelor did not produce malformations in either the rat or rabbit reproductive studies.

Impairment of fertility

Effects on fertility, ability to produce a pregnancy with female partner(s), sperm morphology and sperm motility were observed in the male rat fertility study when cangrelor was administered at human equivalent doses equal to 1.8 fold the recommended PCI dose. These effects were not apparent at lower doses and were reversible following cessation of dosing. In this study, semen analysis was conducted after 8 weeks of continuous treatment.

Female fertility was not affected at any dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Sorbitol
Sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

The powder should be reconstituted immediately prior to dilution and use. Do not refrigerate.
From a microbiological point of view, unless the method of reconstitution/dilution precludes the risk of microbiological contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. For storage conditions after reconstitution and dilution of the medicinal product see section 6.3.

6.5 Nature and contents of container

Powder in 10 mL glass vials (Type 1) closed with a Flurotec coated butyl rubber stopper and sealed with crimped aluminium seal.

Kengrexal is available in packs of 10 vials.

6.6 Special precautions for disposal and other handling

Instructions for preparation

Aseptic procedures should be used for the preparation of Kengrexal.

The vial should be reconsituted immediately prior to dilution and use. Reconstitute each 50 mg/vial 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, colourless to pale yellow solution.

Do not use without dilution. Before administration, 5 mL reconstituted solution has to be withdrawn from each vial and must be diluted further with 250 mL sodium chloride 9 mg/mL (0.9%) solution for injection or glucose (5%) solution for injection. Mix the bag thoroughly.

The medicinal product should be inspected visually for particulate matter after reconstitution.

Kengrexal is administered as a weight-based regimen consisting of an initial intravenous bolus followed by an intravenous infusion. The bolus and infusion should be administered from the infusion solution.

This dilution will generate a concentration of 200 micrograms/mL and should be sufficient for at least two hours of dosing as required. Patients 100 kg and over will require a minimum of two bags.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo, 26/A
43122 Parma
Italy

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/994/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 March 2015
Date of latest renewal: 16 December 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Diapharm GmbH & Co. KG
Am Mittelhafen 56
48155 Münster
GERMANY

Amryt Pharmaceuticals Designated Activity Company
45 Mespil Road,
Dublin 4, D04 W2F1,
IRELAND

Chiesi Farmaceutici S.p.A.
via San Leonardo, 96
43122 Parma,
ITALY

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Kengrexal 50 mg powder for concentrate for solution for injection/infusion
cangrelor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains cangrelor tetrasodium corresponding to 50 mg cangrelor.
After reconstitution 1 mL contains 10 mg cangrelor.
After dilution 1 mL contains 200 micrograms cangrelor.

3. LIST OF EXCIPIENTS

Mannitol
Sorbitol
Sodium hydroxide

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for injection/infusion
10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution and dilution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

The powder should be reconstituted immediately prior to dilution and use. Do not refrigerate. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo, 26/A
43122 Parma
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/994/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Kengrexal 50 mg powder for concentrate
cangrelor
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

50 mg

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Kengrexal 50 mg powder for concentrate for solution for injection/infusion
cangrelor

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Kengrexal is and what it is used for

Kengrexal is an anti-platelet medicine that contains the active substance cangrelor.

Platelets are very small cells in the blood that can clump together and help the blood to clot. Sometimes clots can form within a damaged blood vessel such as in an artery in the heart and this can be very dangerous as the clot can cut off the blood supply (a thrombotic event), causing a heart attack (myocardial infarction).

Kengrexal diminishes the clumping of platelets and so reduces the chance of a blood clot forming.

You have been prescribed Kengrexal because you have blocked blood vessels in your heart (coronary artery disease) and you need a procedure (called a percutaneous coronary intervention – PCI) to remove the blockage. During this procedure you may have a stent inserted in your blood vessel to help to keep it open. Using Kengrexal reduces the risk that this procedure will cause a clot to form and block the blood vessels again.

Kengrexal is only for use in adults.

2. What you need to know before you use Kengrexal

Do not use Kengrexal
- If you are allergic to cangrelor or any of the other ingredients of this medicine (listed in section 6).
- If you have a medical condition that is currently causing bleeding such as bleeding from the stomach or intestines or you have a condition which makes you more prone to uncontrolled bleeding (impaired haemostasis or irreversible coagulation disorders).
- If you have recently undergone major surgery or suffered from any form of serious physical trauma such as a bone fracture or road traffic accident.
- If you have uncontrolled very high blood pressure.
- If you have ever had a stroke, or a ‘mini-stroke’ (also known as a transient ischaemic attack, TIA) caused by the temporary interruption of the blood supply to the brain.

Warnings and precautions
Talk to your doctor before using Kengrexal if:
- You are, or you think you may be at increased risk of bleeding. For example, if you have a medical condition that affects blood clotting or because of another medical condition that may increase the risk of bleeding such as a recent serious injury, any recent surgery, history of a stroke or a transient ischaemic attack or recent bleeding from your stomach or gut.
- You suffer from impaired kidney function or require dialysis.
- You have ever suffered from an allergic reaction to Kengrexal or any of its constituents.
- You suffer from breathing difficulties such as asthma.
- You have been told by your doctor that you have an intolerance to some sugars.

Children and adolescents
Kengrexal is not recommended for children and adolescents under 18 years.

Other medicines and Kengrexal
You may receive acetylsalicylic acid (ASA) while you are treated with Kengrexal or another type of anti-platelet medicine (e.g., clopidogrel) before and after you are treated with Kengrexal.

Tell your doctor if you are taking other medicines that may increase the risk of side effects such as bleeding including blood thinners (anticoagulants e.g. warfarin).

Tell your doctor if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Kengrexal is not recommended for use during pregnancy.

Driving and using machines
The effect of Kengrexal wears off quickly and it is unlikely to affect your ability to drive or to use machines.

Kengrexal contains sodium and sorbitol
Sorbitol is a source of fructose. If you have hereditary fructose intolerance (HFI), a rare genetic disorder, you must not receive this medicine. Patients with HFI cannot break down fructose, which may cause serious side effects.
You must tell your doctor before receiving this medicine if you have HFI.

This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.

3. How to use Kengrexal

Your treatment with Kengrexal will be supervised by a doctor experienced in caring for patients with heart disease. The doctor will decide how much Kengrexal you receive, and will prepare the medicine.

Kengrexal is for injection, followed by infusion (drip), into a vein. The dose given depends 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 (drip), for at least 2 hours. The doctor will decide if you will need to be treated for longer periods.

If you use more Kengrexal than you should
This medicine will be given to you by a healthcare professional. Your doctor will decide how to treat you, including stopping the medicine and monitoring for signs of side effects.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If side effects occur, they may need medical attention.

Tell your doctor **immediately** if you notice any of the following:
- Bleeding from anywhere in the body. Bleeding is a common side effect of treatment with Kengrexal (may affect up to 1 in 10 people). Bleeding can be serious, and fatal outcomes have been reported.
- Allergic reaction (a rash, itching, throat tightening/swelling, swelling of the tongue or lips, difficulty breathing). Allergic reaction is a rare side effect of treatment with Kengrexal (may affect up to 1 in 1,000 people) but may be potentially serious.

Common side effects: may affect up to 1 in 10 people
- Minor bruising can occur anywhere in the body (including small red bruises on the skin or at the site of an injection under the skin causing swelling),
- dyspnoea (shortness of breath),
- bleeding leading to decreases in blood volume or red blood cell numbers,
- fluid discharge from injection or catheter sites.

Uncommon side effects: may affect up to 1 in 100 people
- Bleeding leading to fluid around the heart, blood in the chest cavity or bleeding from the nose, gastrointestinal tract, in the abdomen, or in the urine or from injection or catheter sites,
- increased levels of creatinine in the blood (identified by blood tests), indicating reduced kidney function,
- variations in blood pressure,
- rash, pruritus, urticaria,
- vessel puncture site haematoma.

Rare side effects: may affect up to 1 in 1,000 people
- Bleeding leading to low platelet count or anaemia,
- bleeding in the eye, brain (including stroke), pelvis and lung,
- bleeding from the site of wounds,
- balloon-like swelling in an artery or wall of the heart, which involves only a few layers of the vessel walls,
- severe allergic reactions,
- reduced clotting of the blood,
- bruising,
- swollen face.

Very rare side effects: may affect up to 1 in 10,000 people
- Bleeding under the skin or around the eye,
- infection of bleeding sites,
- heavy menstrual bleeding,
- bleeding from the penis, ear or pre-existing skin tumours.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet.
You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Kengrexal

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after 'EXP'. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Reconstituted solution: the powder should be reconstituted immediately prior to dilution and use. Do not refrigerate.

Diluted solution: From a microbiological point of view, unless the method of reconstitution/dilution precludes the risk of microbiological contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6. Contents of the pack and other information

What Kengrexal contains
The active substance is cangrelor. Each vial contains 50 mg cangrelor. After reconstitution 1 mL of concentrate contains 10 mg cangrelor and after dilution 1 mL of solution contains 200 micrograms cangrelor.
The other ingredients are mannitol, sorbitol and sodium hydroxide for pH-adjustment.

What Kengrexal looks like and contents of the pack
Powder for concentrate for solution for injection/infusion in a glass vial.
Kengrexal is a white to off-white freeze-dried powder.
Kengrexal is available in packs of 10 vials.

Marketing Authorisation Holder
Chiesi Farmaceutici S.p.A.
Via Palermo, 26/A
43122 Parma
Italy

Manufacturer
Diapharm GmbH & CO. KG
Am Mittelhafen 56
48155 Münster
Germany

Amryt Pharmaceuticals Designated Activity Company
45 Mespil Road,
Dublin 4, D04 W2F1,
Ireland

Chiesi Farmaceutici S.p.A.
via San Leonardo, 96
43122 Parma,
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Ferrer Internacional, S.A..
Tél/Tel: +32 15 28 74 15

България
Chiesi Bulgaria EOOD
Тел.: + 359 29201205

Česká republika
Chiesi CZ s.r.o.
Tel: +420 261221745

Danmark
Chiesi Pharma AB
Tlf: +46 8 753 35 20

Deutschland
Ferrer Deutschland GmbH
Tel: +49 (0) 2407 502311-0

Eesti
Chiesi Pharmaceuticals GmbH
Tel: +43 1 4073919

Ελλάδα
Chiesi Hellas AEBE
Τηλ: + 30 210 6179763

España
Ferrer Farma, S.A.
Tel: +34 93 600 3700

France
Bioprojet Pharma
+33 (0)1 47 03 66 33

Hrvatska
Chiesi Pharmaceuticals GmbH
Tel: + 43 1 4073919

Ireland
Chiesi Farmaceutici S.p.A.
Tel: + 39 0521 2791

Ísland
Chiesi Pharma AB
Tlf: +46 8 753 35 20

Italia
Chiesi Italia S.p.A.
Tel: + 39 0521 2791

Lietuva
Chiesi Pharmaceuticals GmbH
Tel: +43 1 4073919

Luxembourg/Luxemburg
Ferrer Internacional, S.A.
Tél/Tel: +32 15 28 74 15

Magyarország
Chiesi Hungary Kft.
Tel.: +36-1-429 1060

Malta
Chiesi Farmaceutici S.p.A.
Tel: + 39 0521 2791

Nederland
Ferrer Internacional, S.A.
Tél/Tel: +32 15 28 74 15

Norge
Chiesi Pharma AB
Tlf: +46 8 753 35 20

Österreich
Chiesi Pharmaceuticals GmbH
Tel: + 43 1 4073919

Polska
Ferrer Internacional, S.A.
Tel.: +48 518 630 955

Portugal
Ferrer Portugal, S.A
Tel: +351 214449600

România
Chiesi Romania S.R.L.
Tel: + 40 212023642

Slovenija
Chiesi Slovenija d.o.o.
Tel: + 386-1-43 00 901

Slovenská republika
Chiesi Slovakia s.r.o.
Tel: + 421 259300060

Suomi/Finland
Chiesi Pharma AB
Tlf: +46 8 753 35 20

Κύπρος
Chiesi Farmaceutici S.p.A.
Τηλ: + 39 0521 2791

Latvija
Chiesi Pharmaceuticals GmbH
Tel: + 43 1 4073919

Sverige
Chiesi Pharma AB
Tlf: +46 8 753 35 20

United Kingdom (Northern Ireland)
Chiesi Farmaceutici S.p.A.
Tel: + 39 0521 2791

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Kengrexal should be administered by a physician experienced in either acute coronary care or in coronary intervention procedures and is intended for specialised use in an acute and hospital setting.

Posology

The recommended dose of Kengrexal for patients undergoing PCI is a 30 micrograms/kg intravenous bolus followed immediately by 4 micrograms/kg/min intravenous infusion. The bolus and infusion should be initiated prior to the procedure and continued for at least two hours or for the duration of the procedure, whichever is longer. At the discretion of the physician, the infusion may be continued for a total duration of four hours, see section 5.1.

Patients should be transitioned to oral P2Y12 therapy for chronic treatment. For transition, a loading dose of oral P2Y12 therapy (clopidogrel, ticagrelor or prasugrel) should be administered immediately following discontinuation of cangrelor infusion. Alternatively, a loading dose of ticagrelor or prasugrel, but not clopidogrel, may be administered up to 30 minutes before the end of the infusion, see section 4.5.

Instructions for preparation

Aseptic procedures should be used for the preparation of Kengrexal.

The vial should be reconsituted immediately prior to dilution and use. Reconstitute each 50 mg/vial 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, colourless to pale yellow solution.

Do not use without dilution. Before administration, 5 mL reconstituted solution has to be withdrawn from each vial and must be diluted further with 250 mL sodium chloride 9 mg/mL (0.9%) solution for injection or glucose (5%) solution for injection. Mix the bag thoroughly.

The medicinal product should be inspected visually for particulate matter after reconstitution.

Kengrexal is administered as a weight-based regimen consisting of an initial intravenous bolus followed by an intravenous infusion. The bolus and infusion should be administered from the infusion solution.

This dilution will generate a concentration of 200 micrograms/mL and should be sufficient for at least two hours of dosing as required. Patients 100 kg and over will require a minimum of two bags.