# Package insert for use in India only

## Cangrelor for injection 50 mg/vial

**CANREAL**

केनरियाल

***To be sold by retail on the prescription of a Registered Medical Practitioner only.***

**PRESCRIBING INFORMATION**

**1. GENERIC NAME**

Cangrelor for injection 50 mg/vial

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Cangrelor for injection 50 mg/vial
Each 10ml vial contains
Cangrelor……..50 mg

**3. DOSAGE FORM AND STRENGTH**

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

**4. CLINICAL PARTICULARS**

**4.1. Indications**

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

**4.2. Posology and Method of Administration**

***Recommended Dosing***

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

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

To maintain platelet inhibition after discontinuation of Cangrelor infusion, an oral P2Y12 platelet inhibitor should be administered. Administer one as described below:

- ✓ *Ticagrelor*: 180mg at any time during Cangrelor infusion or immediately after discontinuation.
- ✓ *Prasugrel*: 60mg immediately after discontinuation of Cangrelor. Do not administer prasugrel prior to discontinuation of Cangrelor.
- ✓ *Clopidogrel*: 600mg immediately after discontinuation of Cangrelor. Do not administer clopidogrel prior to discontinuation of Cangrelor.

***Preparation and Administration***

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

*Preparation*

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

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

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

Reconstituted Cangrelor should be diluted immediately. Diluted Cangrelor 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.

*Method of administration*

Administer Cangrelor via a dedicated IV line.

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

**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 Cangrelor or to any of the component is the formulation.

**4.4. Special Warnings and Precautions for Use**

*Risk of bleeding*

Treatment with cangrelor may increase the risk of bleeding.

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 cangrelor may increase the risk of intracranial haemorrhage. Cangrelor is contraindicated in patients with any history of stroke/TIA

*Cardiac tamponade*

Treatment with cangrelor may increase the risk of cardiac tamponade.

*Hypersensitivity*

Hypersensitivity reactions may occur after treatment with cangrelor. Cases of anaphylactic reactions/shock and angioedema were recorded.

*Risk of dyspnoea*

Treatment with cangrelor may increase the risk of dyspnoea. Most dyspnoea events were mild or moderate in severity and the median duration of dyspnoea was two hours in patients receiving cangrelor.

*Fructose intolerance*

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

**4.5. Drug Interactions**

Thienopyridines

If clopidogrel or prasugrel are administered during cangrelor infusion, they will have no antiplatelet effect until the next dose is administered. Clopidogrel and prasugrel, therefore, should not be administered until cangrelor infusion is discontinued.

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

Cangrelor 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.

**4.6. Use in Special Populations (such as** pregnant women, **lactating women, paediatric patients, geriatric patients etc.)**

***Pregnancy***

Pregnancy Category C.

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

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

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

***Breast-feeding:***

It is not known whether cangrelor is excreted in human milk. A risk to the suckling child cannot be excluded.

***Fertility:***

No effect on female fertility parameters were observed in animal studies of cangrelor. A reversible effect on fertility was observed in male rats treated with cangrelor.

***Elderly***

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

***Paediatric population***

The safety and efficacy of cangrelor in children aged less than 18 years has not been established. No data are available.

***Renal impairment***

No dose adjustment is needed in patients with mild, moderate or severe renal insufficiency.

***Hepatic impairment***

The metabolism of cangrelor is not dependent of hepatic function, so that dosage adjustment is not required for patients with hepatic impairment.

**4.7. Effects on Ability to Drive and Use Machines**

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

**4.8. Undesirable Effects**

The following important adverse reaction of Cangrelor:

- Bleeding

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.

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),

Not known (cannot be estimated from the available data).

| System organ class | ADRs with frequency |
|---|---|
| **Infections and infestations** | Very rare: Haematoma infection |
| **Neoplasms benign, malignant and unspecified (includes cysts and polyps)** | Very rare: Skin neoplasm bleeding |
| **Blood and lymphatic system disorders** | Rare: Anaemia, Thrombocytopenia |
| **Immune system disorders** | Rare: Anaphylactic Reaction (Anaphylactic shock), Hypersensitivity |
| **Nervous system disorders** | Rare: Haemorrhage intracranial[d]* |
| **Eye disorders** | Rare: Eye haemorrhage |
| **Ear and labyrinth disorders** | Very rare: Ear haemorrhage |
| **Cardiac disorders** | Uncommon: Cardiac tamponade (pericardial haemorrhage) |
| **Vascular disorders** | Common: Haematoma <5 cm, Haemorrhage<br>Uncommon: Haemodynamic instability<br>Rare: Wound haemorrhage, Vascular pseudo-aneurysm |
| **Respiratory, thoracic and mediastinal disorders** | Common: Dyspnoea (Dyspnoea exertional)<br>Uncommon: Epistaxis, Haemoptysis<br>Rare: Pulmonary haemorrhage |
| **Gastrointestinal disorders**<br>**Retroperitoneal haemorrhage,** | Uncommon: Retroperitoneal haemorrhage,* Peritoneal haematoma, Gastrointestinal haemorrhage[a] |
| **Skin and subcutaneous tissue disorders** | Common: Ecchymosis (Petechiae, Purpura)<br>Uncommon: Rash, Pruritus, Urticaria[f]<br>Rare: Angioedema |
| **Renal and urinary disorders** | Haemorrhage urinary tract,[e] Acute renal failure (renal failure) |
| **Reproductive system and breast disorders** | Rare: Pelvic haemorrhage, Menorrhagia, Penile haemorrhage |
| **General disorders and administration site conditions** | Common: Vessel puncture site discharge,<br>Uncommon: Vessel puncture site haematoma[b] |
| **Investigations** | Common: Haematocrit decreased, Haemoglobin decreased**<br>Uncommon: Blood creatinine increased<br>Rare: Platelet count decreased, Red blood cell count decreased, International normalised ratio increased[c] |
| **Injury, poisoning and procedural complications** | Common: Haematoma ≥5 cm<br>Rare: Contusion<br>Very rare: 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 101/12565 (0.8%)

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. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/ to report a side effect.

**4.9. Overdose**

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 cangrelor; however, the pharmacokinetic half-life of cangrelor is three to six minutes. Platelet function is restored within 60 minutes of stopping the infusion.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Mechanism of action**

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 signaling and platelet activation.

**5.2 Pharmacokinetic Properties**

Cangrelor is rapidly distributed and metabolized, reaching Cmax within 2 minutes after administration of an intravenous bolus followed by infusion.

Distribution

Cangrelor administration at a dose of 30mcg/kg bolus plus 4mcg/kg/min showed a volume of distribution of 3.9 L. Plasma protein binding of cangrelor is about 97-98%.

Metabolism

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

Elimination

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

Pharmacokinetic/pharmacodynamic relationship(s)

*Special populations*

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

*Weight*

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

*Paediatric population*

Cangrelor has not been evaluated in a paediatric population.

**6. NONCLINICAL PROPERTIES**

**Carcinogenesis**

No carcinogenicity studies were conducted.

**Mutagenesis**

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

**Impairment of Fertility**

Cangrelor had no significant effect on male or female rats fertility treated for 28 days, or on early embryonic development at steady state plasma concentration ($C_{ss}$) of approximately the same as that achieved in the PCI setting at the MRHD [Reference: KENGREAL USFDA Label, dated: Oct 2019].

**7. PHARMACEUTICAL PARTICULARS**

**8.1 Incompatibilities**

None

**8.2 Packing Information**

10mL clear tubular vial USP type-I with 20mm Bromobutyl Igloo OmniflexPlus stopper 20mm aluminium flip off seals.

**8.3 Storage and Handling Instructions**

Do not store above $30^0$C.

**8. PATIENT COUNSELING INFORMATION**

Advise the patient to read package insert.

**9. DETAILS OF MANUFACTURER**

MSN Laboratories Private Limited,
Formulation Division, Unit II,
Sy.no.1277, 1319 to 1324,
Nandigama (Village & Mandal),
Ranga Reddy District
Telangana-509228,
India.

G030027-00

**10. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE**

5/MN/TS/2014/F/G

**11. DATE OF REVISION**

July 2020