Part VI: Summary of the Risk management plan

SUMMARY OF THE RISK MANAGEMENT PLAN FOR KENGREXAL® (CANGRELOR)

This is a summary of the risk management plan (RMP) for Kengrexal®. The RMP details important risks of Kengrexal®, how these risks can be minimised, and how more information will be obtained about Kengrexal® 's risks, and uncertainties (missing information).

Kengrexal summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Kengrexal® should be used.

This summary of the RMP for Kengrexal® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Kengrexal®s RMP.

I. The medicine and what is it used for

Kengrexal® co-administered with acetylsalicylic acid (ASA), is authorised 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. It contains cangrelor as the active substance, and it is given by intravenous infusion; Kengrexal is available as powder for concentrate for solution for injection / infusion.
Further information about the evaluation of Kengrexal®'s benefits can be found in Kengrexal® 's EPAR, including in its plain-language summary, available on the EMA website.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Kengrexal®, together with measures to minimise such risks are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and product information addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute r*outine risk minimisation* measures.

If important information that may affect the safe use of Kengrexal is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Kengrexal® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Kengrexal®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Important Identified risks:	• Serious bleeding
Important Potential risks:	• Inadequate antiplatelet effect of clopidogrel or prasugrel caused by the mistiming of the cangrelor transition to thienopyridines.
Missing information:	• Exposure to cangrelor during pregnancy and lactation; • Use of cangrelor in the paediatric population (<18 years of age); • Use of cangrelor in patients with increased risk of bleeding (eg history of gastrointestinal bleeding, major surgery within 30 days, clinically relevant thrombocytopaenia or anaemia and patients affected by cerebral arteriovenous malformation); • Use of ticagrelor and prasugrel before, during and after the cangrelor infusion.

II.B Summary of important risks and missing information

Important identified risk

Serious bleeding	
Evidence for linking the risk to the medicine	Antiplatelet agents are used to reduce the risk of ischaemic complications. As a function of their anticoagulant activity, they are known to increase the risk of bleeding. During clinical studies, bleeding was the most common AE in cangrelor- versus clopidogrel- treated patients undergoing PCI (a surgical procedure used to unblock narrowed blood vessels that supply the heart).
Risk factors and risk groups	Patients with major bleeding are generally older than patients with minor or no bleeding and more often experience intraprocedural complications such as emergency use of an intra-aortic balloon pump.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.3, 4.4, 4.8 and 4.9* *PL section 2 and 4* Legal status: Special medical prescription and reserved for acute hospital settings. Additional risk minimisation measures: none

Important potential risk

Inadequate antiplatelet effect of clopidogrel or prasugrel caused by the mistiming of the cangrelor transition to thienopyridines	
Evidence for linking the risk to the medicine	Failing to switch to an oral blood-thinning medicine (clopidogrel or prasugrel) at the recommended time (immediately after stopping Kengrexal and in the case of prasugrel up to 1 hour before stopping Kengrexal) the expected effect on blood platelets is not achieved. This may increase the risk of serious or life-threatening blood clots forming in the arteries of the heart in a patient who has just undergone PCI. The main clinical study with Kengrexal showed no increase in the number of patients who developed blood clots in the arteries of the heart when switched from Kengrexal given by injection to oral clopidogrel immediately after stopping Kengrexal.
Risk factors and risk groups	No specific group of patients can be identified who are at an elevated risk of receiving mistimed transition dosing from cangrelor to oral thienopyridines. Should this occur it would be due to physician error.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.2 and 4.5* *PL section 2* Legal status: Special medical prescription and reserved for acute hospital settings. Additional risk minimisation measures: none
Additional pharmacovigilance activities	Post Authorisation Safety Study (PASS) To assess the safety of cangrelor in a real world setting in Italy, when administered in patients with acute coronary syndromes undergoing 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. The safety of cangrelor will be based on the incidence of bleeding and transfusion outcomes in the 30 days post-PCI.

Missing information

Exposure to cangrelor during pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.6 and 5.3* *PL section 2* Legal status: Special medical prescription and reserved for acute hospital settings. Additional risk minimisation measures: none

Use of cangrelor in the paediatric population (<18 years of age)	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.2, 5.1 and 5.2* *PL section 2* Legal status: Special medical prescription and reserved for acute hospital settings. Additional risk minimisation measures: none

Use of cangrelor in patients with increased risk of bleeding (eg history of gastrointestinal bleeding, major surgery with 30 days, clinically relevant thrombocytopaenia or anaemia and patients affected by cerebral arteriovenous malformation	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.3, 4.4, 4.8 and 4.9* *PL section 2* Legal status: Special medical prescription and reserved for acute hospital settings. Additional risk minimisation measures: none

Use of ticagrelor and prasugrel before, during and after the cangrelor infusion	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.2 and 4.5* *PL section 2* Legal status: Special medical prescription and reserved for acute hospital settings. Additional risk minimisation measures: none
Additional pharmacovigilance activities	Post Authorisation Safety Study (PASS) To assess the safety of cangrelor in a real world setting in Italy, when administered in patients with acute coronary syndromes undergoing 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. The safety of cangrelor will be based on the incidence of bleeding and transfusion outcomes in the 30 days post-PCI.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Kengrexal®.

II.C.2 Other studies in post-authorization development plan

Study short name: ARCANGELO (itAlian pRospective study on CANGrelOr)

A multicentre observational, prospective cohort study in patients with acute coronary syndromes undergoing percutaneous coronary intervention who receive cangrelor IV during the procedure transitioning to either clopidogrel, prasugrel or ticagrelor orally (another oral P2Y12 receptor inhibitor).

Purpose of the study:

Antiplatelet therapy is crucial in the treatment of acute coronary syndromes in patients undergoing PCI. Together with acetylsalicylic acid, treatment with P2Y12 inhibitors plays a key role in preventing new cardiovascular events. Because oral P2Y12 inhibitors have some limitations in the acute phase related to delayed onset, variability in gastrointestinal adsorption, and delayed offset when urgent surgery is required, cangrelor appears to be a significant alternative periprocedural treatment. Cangrelor is an intravenous direct-acting and fully reversible P2Y12 receptor inhibitor which, due to its rapid onset and cessation of action, is suitable for patients who are unable to take oral drugs or for whom oral administration is insufficient.

The Champion Phoenix study clearly demonstrated the advantage of cangrelor over clopidogrel (an oral P2Y12 receptor inhibitor considered the gold standard at the time of study design) with a similar safety profile. Due to the lack of evidence compared to the newer oral P2Y12 receptor inhibitors ticagrelor and prasugrel, the European Regulatory Authority requested a post-authorization safety study (PASS), category 3, focusing the treatment of acute coronary syndromes in patients undergoing PCI in order to gather information from real clinical practice to assess safety all oral P2Y12 inhibitors including ticagrelor and prasugrel.

The important potential risk "Inadequate antiplatelet effect of clopidogrel or prasugrel caused by the mistiming of the cangrelor transition to thienopyridines" and the missing information "Use of ticagrelor and prasugrel before, during and after the cangrelor infusion" are addressed through the conduction of the Arcangelo Study.

Primary objective

- To assess the safety of cangrelor in a real-world setting, when administered in patients with acute coronary syndromes undergoing PCI. The safety of cangrelor will be based on the incidence of any haemorrhage at 30 days post-PCI.

Secondary objectives

- To describe the incidence of type 1-2 (mild) and type 3-5 (moderate-severe) bleedings, according to the Bleeding Academic Research Consortium [BARC] both at 48 hours and 30 days post-PCI;
- To assess the efficacy of cangrelor in terms of incidence of major adverse cardiac events (MACE) both at 48 hours and 30 days post-PCI including death, myocardial infarction, ischaemia-driven revascularisation, and stent thrombosis;
- To stratify the results on bleedings and major adverse cardiac events by the specific oral platelet P2Y12 receptor (prasugrel /ticagrelor /clopidogrel);
- To assess the management of transitions from cangrelor to oral platelet P2Y12 receptor, in term of type(prasugrel/ticagrelor/clopidogrel) and timing of administration;
- To describe the use of glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors.