Swiss Summary of the Risk Management Plan (RMP) for 65'335 Kengrexal

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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them. The RMP summary of **Kengrexal** is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the «Arzneimittelinformation» approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document, which is valid and relevant for the effective and safe use of **Kengrexal** in Switzerland, is the «Arzneimittelinformation» (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. **Chiesi SA** is fully responsible for the accuracy and correctness of the content of the here published summary RMP for **Kengrexal**.

Part VI: Summary of the Risk Management Plan by product

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Summary of safety concerns	
Important identified risks	Serious bleeding
	Hypersensitivity
	Dyspnoea
	Renal impairment
Important potential risks	Inadequate antiplatelet effect of clopidogrel or prasugrel caused by the misiming 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 (AVM)]
	use of ticagrelor and prasugrel before, during and after the cangrelor infusion

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
A multicentre retrospective observational study of patients undergoing PCI who receive cangrelor and transition to either clopidogrel, prasugrel or ticagrelor	To describe bleeding and MACE event rates in patients undergoing PCI that require treatment with IV cangrelor switching to either prasugrel or ticagrelor including any association between misiming of	Bleeding and MACE in patients with inadequate antiplatelet effect of clopidogrel or prasugrel caused by the misiming of the cangrelor transition to thienopyridines Bleeding and MACE with the use of ticagrelor and prasugrel before,	Synopsis was submitted along with responses to the Day 180 questions.	Interim safety analysis planned Q4 2016, Q4 2017; Final study report Q3 2018

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	administration of clopidogrel or prasugrel and MACE.	during and after the cangrelor infusion		

VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable.

VI.1.4 Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risk		
Serious bleeding	The proposed SmPC contains the following: Section 4.3 Contraindications Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effect Section 4.9 Overdose	None.
Hypersensitivity	The proposed SmPC contains the following: Section 4.3 Contraindications Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effect	None.
Dyspnoea	The proposed SmPC contains the following: Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effect	None.
Renal impairment	The proposed SmPC contains the following: Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effect Section 5.2 Pharmacokinetic properties Section 5.3 Preclinical safety data	None.
Important Potential Risk		

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Inadequate antiplatelet effect of clopidogrel or prasugrel caused by the mistiming of the cangrelor transition to thienopyridines	The proposed SmPC contains the following: Section 4.2 Posology and method of administration Section 4.5 Interaction with other medicinal products and other forms of interaction	None.
Missing Information		
Exposure to cangrelor during pregnancy and lactation	The proposed SmPC contains the following: Section 4.6 Fertility, pregnancy and lactation Section 5.3 Preclinical safety data	None.
Use of cangrelor in the paediatric population (<18 years of age)	The proposed SmPC contains the following: Section 4.2 Posology and method of administration Section 5.1 Pharmacodynamic properties Section 5.2 Pharmacokinetic properties	None.
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 (AVM)]	The proposed SmPC contains the following: Section 4.3 Contraindications Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effect Section 4.9 Overdose	None.
Use of ticagrelor and prasugrel before, during and after the cangrelor infusion	The proposed SmPC contains the following: Section 4.2 Posology and method of administration Section 4.5 Interaction with other medicinal products and other forms of interaction	None.

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Kengrexal is a blood-thinning medicine used to prevent problems caused by blood clots, such as heart attack. It is used together with aspirin in patients with coronary artery disease (heart disease caused by the obstruction of the blood vessels that supply the heart) who are undergoing percutaneous coronary intervention (PCI – a surgical procedure used to unblock narrowed blood vessels that supply the heart).

Worldwide, coronary artery disease is the single most frequent cause of death. Over seven million people die every year from coronary artery disease, accounting for 12.8% of all deaths. It is estimated

that approximately 1.25 million PCI procedures per year are performed in Europe in patients with coronary artery disease.

VI.2.2 Summary of treatment benefits

Kengrexal contains the active substance cangrelor, which helps prevent blood cells called platelets from sticking together and forming clots. It is given by injection and infusion (drip) into a vein immediately before and during the PCI procedure.

The benefits of Kengrexal were compared with those of oral clopidogrel (another blood-thinning medicine taken by mouth) in one study involving over 11,000 adults with coronary artery disease who were undergoing PCI. Nearly all patients also took aspirin and/or other blood-thinning medicines.

Kengrexal was shown to be beneficial at reducing problems caused by blood clots following PCI; 4.7% of patients (257 out of 5,470) taking Kengrexal had a heart attack, or other problems affecting the heart and blood vessels, or died, compared with 5.9% of patients (322 out of 5,469) taking clopidogrel. Kengrexal was also investigated in one study in which it was given before surgery to patients who had been previously treated with blood-thinning medicines taken by mouth. However, the way this study was designed was considered inadequate to show a clear benefit in these patients, and the company did not pursue this use as part of the application.

VI.2.3 Unknowns relating to treatment benefits

In the clinical studies with Kengrexal, the majority of patients were Caucasians (86%) and male (72%) between 26 and 95 years of age. The types of patients in the studies are typical of those who would be treated with Kengrexal. The safety and effectiveness of Kengrexal has not been studied in patients who are pregnant or breastfeeding, or in patients under 18 years of age.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Bleeding	Treatment with Kengrexal may increase the risk of bleeding. Bleeding is a very common side effect of treatment with Kengrexal (seen in more than 1 patient out of 10). Bleeding can occur anywhere in the body, and it is usually mild varying from oozing, small red bruises on the skin and bleeding at the site of an injection. Bleeding can also be severe, including bleeding from the stomach or intestine, and rarely may cause stroke or death (seen in up to 10 patients out of 10,000).	Kengrexal must not be given to patients who are actively bleeding or are at increased risk of bleeding. It must also not be used in patients who have had a stroke or transient ischaemic attack (mini-stroke). Kengrexal should be used with caution in patients taking medicines that may increase the risk of bleeding, and in patients with diseases that may increase the risk of bleeding. For patients with an unexplained drop in blood pressure or blood haematocrit levels doctors should investigate bleeding as a possible cause. Kengrexal should be used with caution in patients with kidney impairment as these patients are at an increased risk of bleeding. Patients should report any bleeding to their treating doctor. The effect of Kengrexal wears off quickly. If bleeding occurs, appropriate supportive measures should be taken, which may

Risk	What is known	Preventability
		include stopping the medicine so platelet function can return to normal (this is expected to happen within 1 hour of stopping the infusion).
Allergic reactions (hypersensitivity)	Patients treated with Kengrexal may be at risk of experiencing allergic reactions. Seven patients out of 1,000 treated with the medicine experienced some form of allergic reaction, compared with six in 1,000 people in the control group. The allergic reaction varies from rash, itching, swelling of the tongue or lips, throat tightening or swelling, to difficulty breathing.	Kengrexal must not be given to patients who are allergic to cangrelor (the active substance of Kengrexal) or to any of the other ingredients of this medicine.
Difficulty breathing (dyspnoea)	Patients treated with Kengrexal may be at risk of experiencing dyspnoea, also known as shortness of breath, laboured breathing, or other difficulty with breathing. 12 out of 1,000 people treated with Kengrexal experienced some form of dyspnoea, including breathlessness after exercise, compared with 4 out of 1,000 people in the control group. Breathlessness was commonly mild or moderate and lasted around 2 hours.	No specific characteristics have been identified which would place a person at a higher risk of dyspnoea when treated with Kengrexal, and no groups of people have been identified as having a higher risk of breathlessness with Kengrexal. The effect of Kengrexal wears off quickly. If breathlessness occurs, appropriate supportive measures should be taken, which may include stopping the medicine until normal breathing is restored.
Kidney impairment	Animal studies with Kengrexal showed some evidence of kidney injury in rats and dogs, but this occurred at much higher doses or after a longer duration of medicine exposure than those recommended in humans. In the clinical studies, five out of 1,000 patients treated with Kengrexal experienced signs of kidney impairment compared with four in 1,000 patients in the control group. Kidney failure has been reported in between 1 and 10 patients out of 1,000.	Routine measures such as drinking enough water and avoiding contrast agents known to be toxic to the kidneys can help prevent kidney impairment after PCI. Currently it is not known whether or not any measures would effectively reduce the occurrence of kidney impairment in patients after PCI. Patients with severely reduced kidney function are at higher risk of worsening of kidney function and of bleeding when treated with Kengrexal. Kengrexal should be used with caution in these patients.

Important potential risks

Risk	What is known
Inadequate blood-thinning effect of clopidogrel or prasugrel	Failing to switch to an oral blood-thinning medicine (clopidogrel or prasugrel) at the recommended time (immediately after stopping

Risk	What is known
(known as 'thienopyridines') when the switching from Kengrexal to these medicines is not done as per recommendations	Kengrexal and in the case of prasugel 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.

Missing information

Risk	What is known
Use during pregnancy and breastfeeding	Animal studies of Kengrexal showed some effects on fertility and embryo development. These effects were observed at doses much greater than those used in humans and may not be relevant to the use in patients. Nevertheless, Kengrexal should not be used during pregnancy. It is not known whether Kengrexal is excreted in human milk, however this risk cannot be excluded and caution should be exercised when cangrelor is administered to a nursing woman.
Use in patients under 18 years of age	The safety and effectiveness of Kengrexal in patients under 18 years of age has not been established. A clinical study on the use of Kengrexal in this patient population is planned.
Use in patients at increased risk of bleeding [e.g. history of gastrointestinal (gut) bleeding, major surgery within 30 days, clinically relevant thrombocytopaenia or anaemia (low platelet or red blood cell counts), and patients affected by cerebral arteriovenous malformation (AVM – an abnormal connection between the arteries and veins in the brain)]	Kengrexal is known to increase the risk of bleeding in patients undergoing PCI. Patients at increased risk of bleeding should not be given Kengrexal.
Use of ticagrelor and prasugrel before, during and after Kengrexal infusion	No data are available on the use of the oral blood-thinning medicines ticagrelor and prasugrel in patients before, during, and after the use of Kengrexal. Laboratory studies have provided the following information for healthcare professionals to use as a guideline: • Clopidogrel: administer a 600 mg loading dose immediately following discontinuation of Kengrexal infusion • Ticagrelor: administer a 180 mg loading dose immediately following discontinuation of Kengrexal infusion, or optimally

Risk	What is known
	during the infusion • Prasugrel: administer a 60 mg loading dose immediately following discontinuation of Kengrexal infusion, or optimally 30 minutes before the end of the infusion

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet for Kengrexal can be found on Kengrexal's EPAR page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

List of studies in post-authorisation development plan

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
A multicentre, retrospective observational study of patients undergoing PCI who receive cangrelor and transition to either clopidogrel, prasugrel or ticagrelor	To describe bleeding and MACE (major adverse cardiac event) event rates in patients undergoing PCI that require treatment with intravenous cangrelor switching to either prasugrel or ticagrelor including any association between mis-timing of administration of clopidogrel or prasugrel and MACE.	Bleeding and MACE in patients with inadequate antiplatelet effect of clopidogrel or prasugrel caused by the mis-timing of the cangrelor transition to thienopyridines Bleeding and MACE with the use of ticagrelor and prasugrel before, during and after the cangrelor infusion	Planned.	Interim safety analysis planned for Q4 2016, Q4 2017; Final study report: Q3 2018

Studies which are a condition of the marketing authorisation

None.

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable.