Swiss Summary of the Risk Management Plan (RMP)

for

Cardioplexol™, cardioplegic solution

(potassium chloride, magnesium sulphate heptahydrate, procaine hydrochloride, xylitol)

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Disclaimer:

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 minimise them.

The RMP summary of Cardioplexol™ 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 / Information sur le médicament" 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 Cardioplexol™ in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorised by Swissmedic.

Laboratorium Dr. G. Bichsel AG, Weissenaustrasse 73, 3800 Unterseen, as Swiss MAH, is fully responsible for the accuracy and correctness of the content of the published summary RMP of Cardioplexol™, cardioplegic solution.

Summary of risk management plan for Cardioplexol™

This is a summary of the risk management plan (RMP) for Cardioplexol™ (potassium chloride, magnesium sulphate heptahydrate, procaine hydrochloride, xylitol). The RMP details important risks of Cardioplexol™ and how these risks can be minimised.

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

Important new concerns or changes to the current ones will be included in updates of Cardioplexol™ 's RMP.

I. The medicine and what it is used for

Cardioplexol™ is authorised for adults to induce immediate and prolonged diastolic cardioplegic arrest during open-heart surgery performed with miniaturised extra-corporeal circulation (MECC) procedure as well as traditional extra-corporeal circulation (ECC) (see SmPC for the full indication). It contains potassium chloride, magnesium sulphate, heptahydrate, procaine hydrochloride, xylitol as the active substances and it is given by intracoronary injection.

further information about the evaluation of Cardioplexol™ benefits can be found in Cardioplexol™`s Swiss SmPC.

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

Important risks of Cardioplexol™, 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 SmPC 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 *routine risk minimisation* measures.

In the case of Cardioplexol™, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Cardioplexol™ 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 Cardioplexol™. 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.

Table 1: List of important risks and missing information

List of important risks and missing information	
Important identified risks	• Application of insufficient dose
Important potential risks	• Overdose • Intravenous (systemic) administration
Missing information	• None

II.B Summary of important risks

Table 2: Important identified risk: Application of insufficient dose

Important identified risk: Application of insufficient dose	
Evidence for linking the risk to the medicine	Scientific literature. It also seems obvious that incomplete coverage of the myocardium by the cardioplegic solution prevents these areas from being protected from ischemia.
Risk factors and risk groups	No specific group of patients except for those in whom the dose must be repeated, i.e., patients in whom the procedure is more complex and will require a longer aortic clamping time.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC section 4.2 where advice is given that Cardioplexol™ should only be used by trained cardiosurgeons. <u>Additional risk minimisation measures:</u> Training program and continuous medical educational platform for cardiosurgeons and cardiotechnicians available to train themselves to the preparation and handling of Cardioplexol™.

Table 3: Important potential risk: Overdose

Important potential risk: Overdose	
Evidence for linking the risk to the medicine	There is no published evidence of the frequency of overdose of cardioplegic solutions. Overdose is, however, possible and can increase the known risks of this kind of medicinal products.
Risk factors and risk groups	Patients requiring repeated injection of the cardioplegic solution may be at higher risk.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.9 where information is given on monitoring the liver function that overzealous instillation of the solution may result in unnecessary dilatation of the myocardial vasculature and leakage into the perivascular myocardium. Additional risk minimisation measures: No risk minimisation measures.

Table 4: Important potential risk: Intravenous (systemic) administration

Important potential risk: Intravenous (systemic) administration	
Evidence for linking the risk to the medicine	Theoretical considerations. Intravenous injection would have the potential to dramatically increase known risks of this kind of medicinal products.
Risk factors and risk groups	Not applicable
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 where advice is given that Cardioplexol™ is for intracoronary use only and must not be used for systemic infusion. Additional risk minimisation measures: No risk minimisation measures.

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 Cardioplexol™.

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

A registry (phase IV, post authorization safety study) is planned to be initiated as soon as the Cardioplexol™ solution has been registered. Information will essentially focus on a selection of peri-operative data similar to those collected in the study protocol of study SCT-Cpx-004. Among a few others, following parameters / data will be recorded:

Demographic data: Age, gender

Patient's health status: Risk factors including diabetes and renal insufficiency, body mass index (BMI), history of previous cardiac surgery, left ventricular ejection fraction (LVEF).

Cardiac status: LVEF, status post-infarction (date of infarction), hypertrophy, valve conditions.

Surgery data: Date of surgery, name of surgeon, type of surgery, ECC and cardioplegia data (time at ECC begin, time at aortic clamping, time at beginning of initial cardioplegic injection, duration of initial cardioplegic injection, volume of initial cardioplegic injection, time at cardiac arrest, time at beginning of second cardioplegic injection, volume of second cardioplegic injection, time at beginning of third cardioplegic injection, volume of third cardioplegic injection, time at beginning of fourth cardioplegic injection, volume of fourth cardioplegic injection, time at aorta unclamping, time at ECC termination), comments about the cardioplegia procedure and reasons for deviating from the administration protocol. Internal and external defibrillation. Use of an intra-aortic balloon pump (IABP) or another assist device. Adverse events.

Post-surgery data: Status at 24 hours post-reperfusion (dead, alive, still in the intensive care unit (ICU)), time at ICU discharge if discharged within 24 hours, use of an IABP or another assist device. Adverse events. All values of troponin T (TnT), troponin I (TnI), creatinine kinase-myocardial band (CK-MB) and time of assessment.

Each surgeon having successfully completed the Cardioplexol™ specific training program will be requested to participate to the registry and include at least his/her first 5 Cardioplexol™ cases.

It is believed that the conditions offered by the registry participation will motivate surgeons to comply with the protocol of Cardioplexol™ administration. The main objective of this registry is obviously to monitor the compliance with the administration protocol and to be able to react to any possible deviation. It is, however, expected that this registry will also contribute to a better understanding of the value of Cardioplexol™ in specific conditions such as patients with ventricular hypertrophy, patients with LVEF<30%, diabetic patients, or patients with renal insufficiency for example.