

# Autologous Mesenchymal Stem Cells for Cardiac use

## CardioRel™

### Composition

CardioRel™ consists one or more polypropylene cryovials of 1.5 ml autologous human mesenchymal stem cell suspension.

Transport medium for CardioRel™ consists of DMSO, Dextran and human serum albumin in normal physiological saline.

### Description

CardioRel™ is a mesenchymal stem cells (MSCs) preparation for cardiac tissue regeneration. It is prepared from the patient's bone marrow sample after isolating and expanding the mesenchymal stem cells in-vitro, for autologous use. CardioRel™ is a preparation of pure (>80%) cultured autologous MSCs from the adult bone marrow.

CardioRel™ is prepared from bone marrow of suitable patients tested and found negative for HBsAg, and for HIV-1, HIV-2, Hepatitis C, CMV-IgG and IgM and Syphilis antibodies. CardioRel™ is cultured under aseptic conditions. The final product is tested for cell concentration, viability and purity by using appropriate assays and is sterile.

### Mechanism of Action

For the treatment of ischemic pathologies of the heart, many types of cells have been tested as a source of stem cell therapy for the regeneration of damaged myocardial performance. Compared to the other cell types considered for cardiomyoplasty, MSCs present in the bone marrow appear to possess unique properties that may be convenient and clinically useful. MSCs can differentiate into a cardiomyocyte-like phenotype when implanted in the infarcted myocardium.

### Clinical study

An open label, case control prospective study was conducted in 30 patients undergoing CABG. Of these, 15 patients were administered CardioRel™ along with CABG while 15 patients undergoing CABG only, constituted the control group. The data changes from baseline in the area of infarction, ejection fraction and change in ventricular wall movement were noted at baseline and on day 30 and day 60. The mean improvement in the percentage of infarction area as compared to baseline, at the end of 3 months and 6 months related to the arteries in the CardioRel™ group were 35.8 and 32.5% respectively for LAD (left anterior descending artery), 37.7 and 32.5% respectively for LCX (left circumflex artery) and 52.6 and 41.7% respectively for RCA (right coronary artery) whereas in the control group, the values were 11.3 and 16.3% respectively for LAD, 16.0 and 25.6% respectively for LCX and 34.7 and 30.5% respectively for RCA. The mean change in the percentage infarct size from baseline was statistically significant in the case group but not in the control group. The mean change from baseline for the wall motion abnormality was not statistically significant in the CardioRel™ and the control group. The mean change from the baseline in the ejection fraction at the end of 6 months was statistically significant for both the case and the control group. CardioRel™ was well tolerated by the patients. There were no abnormal tissue formations in the heart, as per the 2D echocardiography and scintigraphy reports. No cases of hematological malignancies were reported. There were no deaths or discontinuation due to the treatment. Hypokalemia was the most common adverse effects seen (8 patients in the CardioRel™ group and 7 in the control group). The other adverse events seen were tachycardia, fever, acidosis and extrasystoles. Overall, CardioRel™ appears to have a safety profile similar to other cell based therapies currently being explored for ischemic heart disease.

### Indication

CardioRel™ is indicated in patients undergoing Coronary Artery Bypass Graft for the treatment of myocardial infarction and having LV dysfunction and regional cardiac wall motion abnormality.

### Contraindications

- Presence of cardiogenic shock at presentation
- Presence of any type of arrhythmia on 12-lead electrocardiography (12-lead ECG) and/or Holter monitoring
- Presence of LV aneurysm
- Presence of any coagulation abnormalities
- Presence of a primary hematological disease
- Previous or current history of neoplasia or other co-morbidity that could impact the patient's short term survival

### Use In Specific Populations

#### Pregnancy and Lactation

No studies have been performed till date in pregnant women; therefore transplant should be done in pregnant women only if clearly needed and as judged by the surgeon.

#### Pediatric and Geriatric Population

Our studies have been performed in adults between 34 to 74 years of age, therefore transplant should be done in other cases based on the judgement of the cardiovascular surgeon.

#### Dosage and Administration

CardioRel™ should be administered by ten injections in the peri-infarct area of the scarred myocardium during the CABG at a dose of 0.1 ml per injection. The total dose will be between  $5 \times 10^7$  and  $300 \times 10^7$  cells per patient.

#### Warning

CardioRel™ is a biological product and is therefore perishable.

#### Usage precautions

- CardioRel™ is to be used by cardiac surgeons only.
- Post-operative monitoring should be similar to that undertaken for CABG.
- CardioRel™ is for single use only.
- The container with the product should be opened only in the operation theatre as per usage guidelines.
- Please read the USER GUIDELINES prior to application.
- Thawing of CardioRel™ should be done in the operation theatre just prior to injection.
- CardioRel™ should be used immediately after thawing.
- Once thawed, CardioRel™ cannot be re-frozen and will have to be discarded.

#### Handling procedure for CardioRel™

- Open the thermacol box and check if there is adequate quantity of dry ice in the box and the vials are well buried in that. CardioRel™ vials should be in frozen condition.
- Check the integrity of the vial. Do not use the vial if it is cracked, damaged or opened.

#### Thawing procedure for CardioRel™

- Thaw the vials in the operation theatre just prior to injection.
- Remove the vial from the dry ice and swab the exterior with ethanol or suitable disinfectant.
- Place the vial in warm water (37°C), agitating it gently until completely thawed. Ensure that the vial is not completely immersed in the water.
- Rapid thawing (60 – 90 seconds at 37°C) provides best recovery of stem cells.
- Once thawed, remove the vial from water and de-contaminate the surface by spraying with disinfectant.
- As soon as the contents are thawed, ask the surgeon's assistant to aspirate all the content into a syringe.
- CardioRel™ should be immediately administered after thawing.

#### Storage conditions

CardioRel™ must be frozen and stored at -196°C till it is despatched. The transport is done at -70°C to -80°C in dry ice and must be stored frozen in dry ice at -70°C to -80°C on arrival at the site of transplant. Prior to injection, CardioRel™ cryovial will first be thawed rapidly by immersing in a 37°C water bath and injected immediately. If it is not to be used immediately, then it should not be thawed. Once thawed, it has to be used immediately. After arrival at the site, it has to be kept in Liquid nitrogen (-196°C) till the time of use or if there are no facilities, it may be kept in dry ice upto 48 hrs. Viability beyond 48 hrs in dry ice is not assured.

#### Contents of kit

CardioRel™ kit contains cryovials containing Autologous Mesenchymal stem cells in dry ice.