REGENACIP® 200M Injection for CLI PAD (Adult human bone marrow derived, cultured, pooled allogeneic Mesenchymal Stromal Cells)

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Qualitative and Quantitative Composition

REGENACIP®

Each cryobag contains:

Mesenchymal stromal cells……200 million/15 mL

The excipients (inactive ingredients) are 10% dimethyl sulfoxide, 5% human serum albumin solution and 85% multiple electrolyte solution.

Dosage Form and Strength

Intramuscular injection

REGENACIP® is a formulation of Adult human bone marrow derived, cultured, pooled allogeneic Mesenchymal Stromal Cells (BMMSCs) intended for intramuscular injection (IM) only.

REGENACIP® is provided as a frozen cell suspension in a cryobag containing 200 MSCs per 15 mL.

Clinical Particulars

Therapeutic Indication

Atherosclerotic Peripheral Artery Disease patients with established critical limb ischemia in Rutherford III-5 or III-6, not eligible for or have failed traditional revascularization treatment, with rest pain and / or ulcers in the affected limb.

Posology and Method of Administration

Posology

Pre-treatment

It is recommended to administer premedication of appropriate dosage of IV steroid (e.g., 100mg of hydrocortisone) and antihistaminic (e.g., 45.5mg pheniramine maleate) within one hour prior to injection of **REGENACIP®**. This is to prevent any potential hypersensitivity reaction after

administration of **REGENACIP®,** which is characterized by fever, chills, rash and hypotension. However, there has not been any report of hypersensitivity reaction in clinical trials conducted using **REGENACIP®**.

Method of calculating dose

Dosing of **REGENACIP®** is based on body weight. The recommended dose of 2 million cells/kg body weight administered as 0.6 ml/kg of the reconstituted product intramuscularly (IM).

Cell dose = Patient body weight (kg) X 2 million cells

Total volume to be administered = Patient body weight (kg) X 0.6 ml.

Administration

REGENACIP® should be administered by a qualified physician who is trained in the management of peripheral arterial diseases.

Reconstitution Procedure

There is 200 Million mesenchymal stromal cells in each cryobag in a total volume of 15 ml.

Aluminium cassette containing the cryobag of **REGENACIP®** is taken out from dry shipper using cryogloves. Remove **REGENACIP®** from the cassette and immerse the **REGENACIP®** bag into a water bath containing sterile distilled water at 37°C. Do not squeeze or break the frozen **REGENACIP®** cryobag during the thawing process. The bag should be gently rocked to mix the suspension for 3 to 4 minutes till it thaws. Aseptically add 35 ml of multiple electrolyte solution (supplied along with **REGENACIP®**) into the cryobag using a syringe with 18-gauge needle to make up the volume to 50 ml. Thus, the bag in the final suspension contains 200 million cells per 50 ml or 2 million cells per 0.6 ml.

Caution:

- Cryoprotective gloves are to be used for handling the frozen cryobags
- Handle the frozen cryobags gently and avoid sudden shocks and jerks to avoid leakage of the frozen cryobags.

Reconstitution summary:

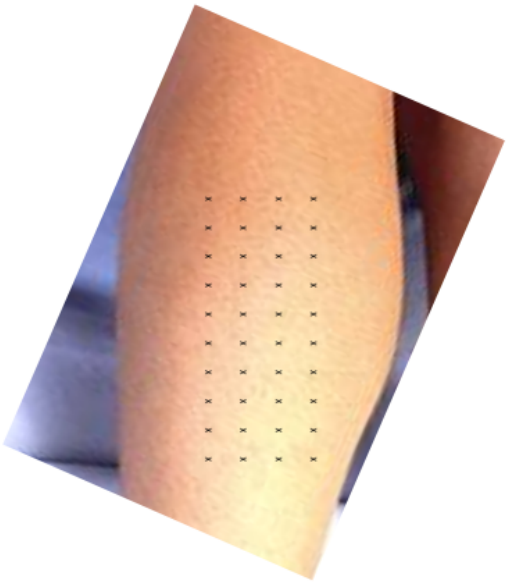
Dose	**REGENACIP® bag to be used**	**Diluent for Reconstitution**
2 million cells/kg body weight or 0.6 ml/kg of the cell suspension	200 million cells/15 ml	Add 35 ml multiple electrolyte solution (Plasmalyte A or equivalent) to the cryobag of 200 million in 15ml suspension to make up the final volume to 50 ml

Method of Administration

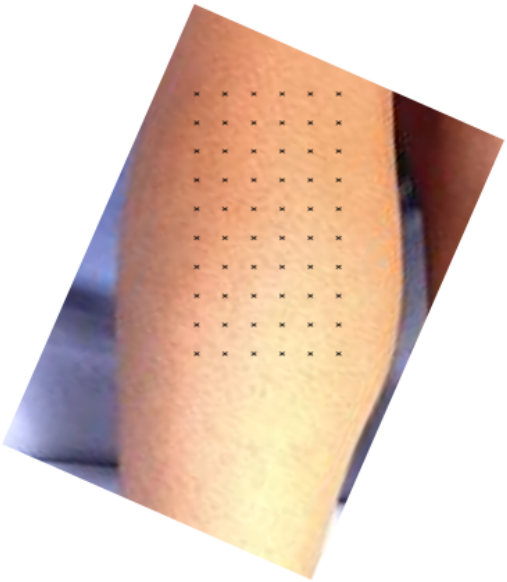
1. Shake the reconstituted cryobag gently before use.
2. Do not add any other medicines to the contents of the cryobag.
3. Administer the reconstituted product through disposable sterile syringes.
4. Use the product within 60 minutes after reconstitution.
5. The product is to be administered intramuscularly (IM) as 40 to 60 multiple injections in the

gastrocnemius muscle in a volume of 0.5 to 1 ml per injection. Injection points are to be separated by 1 cm from each other. In case of ulcers, 2 ml (200 million bag) (out of the total calculated volume for the patient) is to be administered around the ulcers as multiple intramuscular injections.

Note: It is recommended that REGENACIP® administration be performed preferably under IV sedation with cardio-respiratory monitoring. Spinal, epidural or short general anaesthesia may be considered as per the physician's/anaesthetist's advice.



10 X 4 grid – To administer 40 injections



10 X 6 grid – To administer 60 injections

Contraindications

1. Patients with known hypersensitivity to dimethyl sulfoxide (DMSO) or human serum albumin (HSA).
2. Patients with known sensitivity to porcine (pig) or bovine (cow) products.

Special Warnings and Precautions for Use

Caution should also be used when administering **REGENACIP®** to patients with a known sensitivity to porcine (pig) or bovine (cow) products, because trace amounts of these components used in manufacturing may be present in the final product.

It is recommended that oxygen saturation (SaO2/SAT) is monitored by pulse oximetry during infusion of the product and 2 hours thereafter.

Risk of Transmission of Infectious Agents

REGENACIP® is a pooled product from healthy volunteer bone marrow donors. The possibility of transmission of infectious agents cannot be completely excluded as with any blood or marrow derived product. Stempeutics Research has taken specific measures to reduce this potential risk as

outlined below:

- Rigorous donor screening including physical exam and medical history
- Donor testing for infectious diseases including Human Immunodeficiency Virus (HIV)-1 and II, hepatitis B and hepatitis C viruses, Human T Lymphotropic Virus (HTLV), Syphilis, Cytomegalovirus (CMV), Epstein Barr Virus (EBV) and Parvovirus B-19. Certain of these tests are repeated during manufacturing.
- Use of reagents in manufacture that are sterile and have undergone viral inactivation where appropriate. Bovine serum used in the manufacturing process is carefully sourced from TSE-BSE free countries to minimize the risk of TSE-BSE infectivity.
- During the manufacturing process, testing for viral and adventitious agents is performed, including sterility, endotoxin and mycoplasma testing.
- At the end of processing, final testing for viral and adventitious agents is performed, including sterility, endotoxin and mycoplasma.
- All of the testing must be negative before the product can be released for use.

Risk of Hypersensitivity

Patients with known hypersensitivity to the constituents of the IMP – dimethyl sulfoxide (DMSO) or human serum albumin (HSA) might develop hypersensitivity reaction characterized by fever, chills, rash and hypotension.

To reduce this potential risk of hypersensitivity, patients should be monitored for signs and symptoms of hypersensitivity reaction while on treatment with **REGENACIP®.**

Caution should also be used when administering **REGENACIP®** to patients with a known sensitivity to porcine (pig) or bovine (cow) products, because trace amounts of these components used in manufacturing may be present in the final product.

It is recommended that oxygen saturation (SaO2/SAT) is monitored by pulse oximetry during infusion of the product and 2 hours thereafter.

Drug Interactions

This medicinal product must not be mixed with other medicinal products.

Drug-Laboratory Interactions

There is no evidence from preclinical or clinical studies that **REGENACIP®** has a direct effect on laboratory test

Drug-Drug Interactions

No specific drug interaction studies have been conducted with **REGENACIP®**. No clinically relevant drug interactions have been reported when **REGENACIP®** was administered with analgesics, vasodilators, statins and prostacyclin analogue in clinical trials.

The effects of lifestyle choices such as smoking and alcohol consumption on **REGENACIP®** have not been established.

Patients suffering from critical limb ischemia are on several medications including analgesics. To date, there are no reports of any drug interaction with **REGENACIP®** in clinical trials.

Drug-Food Interactions

There have not been any reports of food interactions with **REGENACIP®**. BMMSCs are naturally occurring cells in the body and would not be expected to have any interactions with food.

Use in Special Populations

Patients with Hepatic or Renal Impairment

Data on the use of **REGENACIP®** in patients with hepatic or renal impairment is not available, however, given the cell – based nature of **REGENACIP®** and being locally administered by intramuscular route it is not expected that the benefit – risk profile of **REGENACIP®** in patients with hepatic or renal impairment will differ from that observed in patients with normal hepatic or renal function. Therefore, no dose adjustment is required in hepatic or renal impairment.

Pregnant Women

Pregnant women have been excluded from **REGENACIP®** clinical trials, therefore guidance on treating these patients cannot be provided. **REGENACIP®** is not recommended in women of childbearing potential not using contraception.

Lactating Women

Breast feeding women have been excluded from **REGENACIP®** clinical trials, therefore guidance on treating these patients cannot be provided.

Pediatric Patients (below 18 years)

The safety and efficacy of **REGENACIP®** in children below 18 years have not yet being established. No data are available.

Geriatric Patients (65 years or above)

Data on use of **REGENACIP®** in the elderly population are limited, however, given the cell – based nature of **REGENACIP®** and its local administration by intramuscular route, it is not expected that the benefit – risk profile of **REGENACIP®** will differ from that observed in non – elderly patients. Therefore, no dose adjustment is required in elderly patients.

Ethnicity

REGENACIP® has been tried in Indian ethnic population and no data exists of being injected in different ethnic groups. Seeing the safety profile of mesenchymal stromal cells it is expected that the safety profile of **REGENACIP®** will not differ in different ethnic populations.

Undesirable Effects of REGENACIP®

The adverse events observed in clinical trials evaluating **REGENACIP®** in critical limb ischemia have been primarily the manifestations of the underlying disease. Common adverse events seen in clinical trials are: skin ulcer, pyrexia, wound infection, gangrene. The treatment given for these adverse effects in critical limb ischemia due to atherosclerotic peripheral artery disease includes but not limited to analgesics, vasodilators, statins and prostacyclin analogue amongst others.

Post-Marketing Experience

Nil

Reporting of side effects

If you get any side effects, talk to your doctor, or nurse write to drugsafety@cipla.com. You can also report side effects directly via the National Pharmacovigilance Program of India by calling on 1800 180 3024 or you can report to Cipla Ltd. on 1800 267 7779.

By reporting side effects, you can help provide more information on the safety of this product. **This includes any possible side effects not listed in this leaflet.**

You can report side effects directly to:

Pharmacovigilance Programme of India National Coordination Centre, Indian Pharmacopoeia Commission, Ministry of Health & Family Welfare, Govt. of India Sector-23, Rajnagar, Ghaziabad-201002.UttarPradesh Tel.:0120-2783400, 2783401, 2783392 FAX: 0120-2783311 Email: pvpi.compat@gmail.com	**Cipla Ltd.** Email: drugsafety@cipla.com
Toll Free number: 1800-180-3024 (9 am to 5.30 pm weekdays).	Toll-free number :1800 267 7779

Overdose

Overdose has not been reported in clinical trials till date and the maximum tolerated dose of **REGENACIP®** has not been established in humans. Doses up to 2 Million BMMSC's (**REGENACIP®**) /kg have been administered to patients in clinical trials without dose limiting toxicity.

Pharmacological Properties
Mechanism of Action

The mechanism of action of **REGENACIP®** is likely to be due to a combinatorial effect of anti-inflammation and pro-angiogenic activity governed by paracrine function or by directly producing the factors (VEGF, angiopoietin, IL-6, IL-8, PGE2 amongst others) at the site of inflammation and ulcer location. **REGENACIP®** may also stimulate the migration of host endothelial cells to the ischemic tissues which in turn lead to neoangiogenesis by these cells which integrate to form new blood vessels. In fact we have shown in in vitro studies that **REGENACIP®** secreted angiogenic cytokines exert the angiogenic potency, which has been validated through various functional assays such as Human Umbilical vein endothelial cell (HUVEC) migration, proliferation and differentiation to tubes on growth factor reduced matrigel. This leads to increased blood flow in the affected limb thus relieving rest pain and leads to healing of the ulcer.

Pharmacodynamic Interactions

REGENACIP® is a source of numerous angiogenic/arteriogenic cytokines like vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), monocyte chemoattractant protein 1 (MCP-1), placental growth factor, interleukins 1 and 6, insulin-like growth factor, stromal derived factor (SDF-

1), matrix metalloproteinase 9 (MMP-9), hepatocyte growth factor (HGF) and several insulin growth factors. Media collected from MSC cultures promoted in vitro proliferation and migration of endothelial cells. Preclinical animal model study of critical limb ischemia has been done in a BALB/c nude mice model. After local injection, the animals were followed up for 4 weeks and they showed reduction (43%) of necrosis of the foot in the **REGENACIP®** treated group as compared to the placebo group. Safety pharmacology studies in rats and rabbits have demonstrated that **REGENACIP®** is safe upto 10 times human therapeutic dose (20 million cells/kg body weight).

Pharmacokinetic Properties

REGENACIP® is administered intramuscularly (IM) in the calf muscle and locally around the site of ulcer in critical limb ischemia (CLI) due to atherosclerotic peripheral artery disease patients. Pharmacokinetic data of **REGENACIP®** is limited to biodistribution study findings in animals.

The biodistribution kinetics of CM-DiI labelled **REGENACIP®** was studied after intramuscular administration in normal and diseased (hind limb ischemia) BALB/c mice. It showed that intramuscular injection of cells persist only at the injection site for the study duration of 28 days and did not get distributed to other organs. The biodistribution intensity data analysis revealed that the signal intensity peaked at day 1 in sham animals with CM-DiI labelled cells, whereas in limb ischemia (LI) animals injected with CM-DiI labelled cells, the signal intensity peaked on day 6. Thereafter, the signal intensities declined progressively in both groups. At day 28, there were no signal detected in sham animals treated with labelled cells, however, some signal was still detected in the ischemic animals. The mean percentage of signal intensity in the ischemic animals was 12% at day 28 compared to the highest level observed on day 6. Thus, in conclusion, the biodistribution study suggests that intramuscularly injected labelled **REGENACIP®** predominantly stay localized at the injection site in both groups of animals although the kinetics of their distribution varied to a certain extent between the sham control and the ischemic animals.

Nonclinical Properties

Animal Toxicology and Pharmacology

Single dose acute and sub-chronic toxicity studies were done in rodent and non –rodents animals and they were followed for two weeks or three months respectively after administration of **REGENACIP®**. NOAEL was observed with **REGENACIP®** in dose upto 10 times the therapeutic dose (20 million cells / kg body weight). It was also found to non – genotoxic, non – teratogenic and showed no immunological reactions.

Tumorigenicity study was performed in in SCID mice divided using **REGENACIP®** by SC and IM injections and the animals were followed up for 6 months. There was no evidence of tumor formation attributed to **REGENACIP®**. In addition, there has been no evidence of tumor or ectopic tissue formation in long-term subchronic toxicity studies (up to 3 months) in rat and rabbit model. No cases of ectopic tissue formation were reported due to **REGENACIP®** administration in clinical studies.

In a pre-clinical efficacy study in which hind limb ischemia was induced by extended femoral ligation in BALB/c nude mice. A total of 33 murine models were divided into 4 groups: sham control (3 animals), vehicle (10 animals), **REGENACIP®** IMP1 (10 animals) and **REGENACIP®** IMP1A (10 animals). After ligation, animals were injected IM with **REGENACIP®** IMP1 & IMP1A (5×10^6 cells in 50µl of PlamaLyteA) or vehicle alone. Sham control animals underwent the same procedure without any ligation served as a normal control and all the animals were observed for 28 days.

Results demonstrated that while vehicle injected control animals showed 100% foot necrosis (10 out of 10), animals treated with both **REGENACIP®**IMP1 & IMP1A showed significant protection against foot necrosis (70% and 80% protection respectively). Histological evaluation of different hind limb muscles showed significant reduction in necrosis, degeneration and inflammation. The data also clearly demonstrated improvement in muscle fiber area. In conclusion, both **REGENACIP®**IMP1 & IMP1A have comparative potential therapeutic application in ameliorating ischemia induced limb necrosis and muscle degeneration, ultimately leading to limb salvage.

Clinical Properties

Peripheral arterial disease (PAD) is a common disorder and a major cause of morbidity and mortality. The most severely affected patients, with rest pain, ulcerations, or gangrene, are given a diagnosis of critical limb ischemia (CLI). These patients have a particularly poor prognosis, with high rates of limb amputation and mortality.

REGENACIP® has been studied in 3 clinical trials and 1 phase IV study of critical limb ischemia. The first trial CLI Phase I/II (SRPL/CLI/07-08/001) was a double blind placebo controlled trial in 20 patients suffering from critical limb ischemia. Patients received **REGENACIP®** or placebo (Multiple Electrolyte Solution) as multiple intramuscular injections in the gastrocnemius muscle of affected limb. Follow-up evaluations were done at 1 week, 1, 3, 6, 12 and 24 months. The second trial was CLI due to Buerger's disease, a Phase II (SRPL/CLI/09-10/001) study which was non-randomized, open label, dose finding control study evaluating different dose levels of **REGENACIP®** in patients with CLI due to Buerger's disease. Thirty six patients each were accrued in 1 million cells/kg and 2 million cells/kg dose groups and 18 patients were accrued in the control group. Patients in the cell group received the respective dose of **REGENACIP®** in the calf muscle of the affected limb and 2 ml of the drug around ischemic ulcers. Control arm received standard protocol of care alone without placebo injections. Six months follow-up data is presented in this document. Patients are being followed up till the end of 2 years. The third study was a Phase III Label extension study of **REGENACIP®** in patients with CLI due to Atherosclerotic Peripheral Arterial Disease (SRPL/CLI/17-18/002). The study was conducted in 24 patients and the patients are being followed up for a duration of one year. The fourth study was a single arm, multicentric, Phase IV study was to assess the safety and efficacy of intramuscular administration of **REGENACIP®** in patients with critical limb ischemia due to Buerger's disease (version 03 dated 05th Dec 2017). A total of 50 patients were recruited into the study and will be followed up for one year for both safety and efficacy of **REGENACIP®** and for further three years for safety.

CLI I/II study: The safety profile of **REGENACIP®** was comparable to that of placebo in study SRPL/CLI/07-08/001. None of the serious adverse events were related to **REGENACIP®** as per the investigators and the independent data safety monitoring board. **REGENACIP®** has been shown to be efficacious as evidenced by increase in the ankle brachial pressure index (ABPI) from 0.56 to 0.77 in the cell arm as compared to 0.59 to 0.6 in the control arm during the 6 months follow-up (P = 0.0169).

CLI II study: Similarly, the safety profile of both the 1 million cells/kg and 2 million cells/kg body weight groups were comparable to that of control group. All the adverse events were manifestations of the primary illness. All serious adverse events were not related to **REGENACIP®** as per the investigators.

The rest pain decreased from 7.03 units to 1.54 units in the 2 million cells/kg dose group as compared to the control arm 6.66 units to 3.26 units (P = 0.0193) over a period of 6 months. The rate of ulcer healing per month was significant in the 2 million cells/kg dose group (4.09 cm^2

reduced to 0.21 cm^2 as compared to control 1.78 cm^2 reduced to 0.12 cm^2 over a period of 6 months follow-up (P=0.0253)).

REGENACIP® increased the blood flow in the lower limbs as evidenced by significant increase in ankle brachial pressure index in the 2 million cells/kg dose group (increased from 0.47 to 0.66 as compared to control (0.68 to 0.67, P=0.0132) per month over a period of 6 months follow-up.

The total walking distance in the 2 million cells/kg dose group increased from 0.24 km to 0.77 km in the 2 million cells/kg dose group per month (P=0.0577).

CLI Phase III study: The third clinical trial was a Phase III Label extension study of **REGENACIP®** in patients with CLI due to Atherosclerotic Peripheral Arterial Disease. The study was conducted in 24 patients.

One patient withdrew consent and the remaining 23 patients completed 6 month follow-up after the drug administration. The 6 month follow up data of the study confirmed safety and efficacy of the drug. Only 1 SAE was reported during the 6 month follow up and it was assessed to be unrelated to the drug.

The drug at a dose of 2 million cells / kg body weight showed statistical significant improvement in majority of the efficacy parameters which includes, relief of rest pain, healing of ulcers, increase in ankle systolic pressure and ABPI, increase in total walking distance and improvement in QOL over a period of 6 months:

Rest Pain: Rest pain score showed gradual and sustained decrease over the period of six months. In mITT population, the mean (SD) rest pain score reduced from 8.0 (1.57) at baseline to 4.6 (2.17) at 1 month, 2.8 (1.87) at 3 months and 1.7 (2.22) at 6 months which were statistically significant (p value < 0.0001).

Ulcer Healing: Ulceration in the target limb showed gradual and sustained decrease along with complete healing over a period of six months. In the mITT population, the mean (SD) ulcer size reduced from 3.98 (2.524) at baseline to 0.64 (2.126) at 6 months (visit 6) which were statistically significant (p<0.0001).

Ankle systolic pressure: Ankle systolic pressure showed an increase over the study period of 6 months. In the mITT population, the mean (SD) ankle systolic pressure increased from 61 (22.1) mmHg at baseline to 94 (25.3) at 6 months (visit 6) which were statistically significant (p=0.0002).

Ankle Brachial Pressure Index: The ABPI showed gradual and sustained increase over the study period of six months. In the mITT population, the mean (SD) ABPI increased from 0.47 (0.156) at baseline to 0.70 (0.156) at 6 months which was statistically significant (p value < 0.0001).

Total Walking Distance: The total walking distance of patients showed an increase over the study period of six months. In the mITT population, the mean (SD) total walking distance increased from 0.22 (0.254) at baseline to 0.64 (0.555) at 6 months which were statistically significant (p value=0.0002).

Quality of Life (Total Score): Total score for quality of life showed an increase over the study period of 6 months. In the mITT population, the mean (SD) total score for quality of life increased from 2.39 (0.712) at baseline to 4.92 (1.185) at 6 months (visit 6) which were statistically significant (p<0.0001).

CLI Phase IV study: **REGENACIP®** was observed to both safe and efficacious in the study. All

adverse events reported in the study were not related to **REGENACIP®**. The efficacy data showed that rest pain scores significantly reduced from 7.8 (1.31) at baseline to 2.1 (2.19) at 6 months follow up ($p<0.0001$). There was significant mean reduction of 44% of rest pain at 1 month follow up which increased to 72% reduction at 6 months follow up ($p<0.0001$). At 6 months follow up, 68% of the ulcers completely healed ($p<0.0001$) and 20% of the ulcers partially healed. Overall, there was significant decreasing pattern shown in the ulcer healing status (0.59 units per month) ($p <0.0001$). ABPI significantly increased from 0.44 (0.125) at baseline to 0.76 (0.191) at 6 months follow up ($p<0.0001$). There was significant increase in ABPI to 46% at 1 month follow up which increased to 74% at 6 months follow up ($p<0.0001$).

Description

REGENACIP® is a formulation of adult human bone marrow derived, cultured, pooled allogeneic mesenchymal stromal cells (BMMSCs) intended for intramuscular injection (IM) only. **REGENACIP®** is provided as a frozen cell suspension in a cryobag containing 200 MSCs per 15 mL.

The mesenchymal stem cells are derived from the bone marrow of unrelated healthy adult donors. **REGENACIP®** is manufactured under aseptic conditions in a process of isolation and culture expansion under strict GMP compliance. Each batch of **REGENACIP®** is tested against the predefined specifications and is released by Quality Assurance, after meeting the acceptance criteria of in-house specification.

Pharmaceutical Particulars

Incompatibilities

This medicinal product must not be mixed with other medicinal products.

Shelf-Life

REGENACIP® has an established shelf life of 18 months for 200 million cells bag from the date of manufacturing. The reconstituted product should be used within one hour from thaw.

Storage and Handling Instructions

Personnel receiving the cryoshipper containing **REGENACIP®** shall ensure the following, prior to product usage:

- The cryobag in the cryoshipper should be used within ‘Use Before’ date mentioned in the label of the dry shipper. If not used, the shipment to be returned to Stempeutics Research Private Limited. Appropriate documentation is received along with the consignment and is as per the requirement.
- Cryoshipper is received in sealed and good condition, there is no external visible damage to the cryoshipper, data logger is attached and temperature display is within -185°C to -196°C.
- Store **REGENACIP®** at -185°C to -196°C in vapour phase of liquid nitrogen for long term storage at site or proceed for usage if it is planned to use immediately.

Packaging information

200 Million Cells in 15 mL of suspension.

Patient Counseling Information

(Package leaflet: Information for the patient)

REGENACIP®: 200 Million Cells in 15 mL of suspension for injection

1. This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side - affects you may get. See the page 13-14 for how to report side effects.
2. Read all this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or surgeon.
- If you get any side effects, talk to your surgeon or doctor. This includes any possible side effects not listed in this leaflet.

1. What is in this section of the leaflet
   a. What **REGENACIP®** is and what it is used for
   b. What you need to know before you are given **REGENACIP®**
   c. How **REGENACIP®** is given
   d. Possible side effects
   e. How to store **REGENACIP®**
   f. Contents of the pack and other information
2. **What REGENACIP® is and what it is used for**

REGENACIP® is a medicine used for the treatment of critical limb ischemia due to atherosclerotic peripheral artery disease. It is a disease in which the arteries of the legs get blocked due to fatty deposits and blood supply to the limbs is insufficient to maintain their normal functioning. Critical limb ischemia is said to have developed when the blood flow to the limb is insufficient for metabolism of the cells in the limb, even when the person is resting. Those who suffer from critical limb ischemia may experience pain in the feet or in the toes when walking and in some severe cases even at rest. If the disease is severe, they may develop painful sores on the toes or feet. If the circulation does not improve, these ulcers can start as dry, gray, or black sores, and eventually become dead tissue (called gangrene) and it may lead to amputation of the limb.

REGENACIP® when administered can help in development of new vascular endothelial cells (blood vessel cells), which would aid therapy by improving blood supply to the affected limb or its part. This treatment may allow formation of new blood vessels and increase in the blood supply to the affected limbs in critical limb ischemia patients, hence helping to improve walking, also may help in fast healing of ulcers and decrease the rate of amputation; thus improving the quality of life in the affected population.

The active ingredient of **REGENACIP®** is mesenchymal stromal cells which are taken from the bone marrow of a healthy voluntary donor (so called allogenic stem cells) and then expanded in the laboratory. Adult stem cells are a special type of cells found in many adult tissues, whose primary role is the repair of the tissue in which they are found.

1. **What you need to know before you are given REGENACIP®**

You must not be given REGENACIP®

- If you are allergic to porcine (pig) or bovine (cow) products or any the ingredients of this medicine

Warnings and precautions

Talk to your doctor or surgeon before you are given **REGENACIP®**

- **REGENACIP®** is a living cell therapy and, therefore, the final product cannot be sterilised. The product is checked at different stages during its manufacture to ensure that it is free of infection. It is also checked for sterility before it is released, and if it is free of infection, the product is released for use in patients. If after the procedure you feel ill or have fever, inform your physician as soon as you can.

1. **How REGENACIP® is given.**

You may have had an initial discussion with the surgeon prior to **REGENACIP®** administration. The following information is related to the day when **REGENACIP®** is administered.

REGENACIP® is injected by surgeon / vascular surgeon / cardio-thoracic surgeon in the calf muscle of the affected limb and around the ulcer (if any).

The recommended dose is 2 million cells / kg body weight.

On the day of injection of **REGENACIP®**, the physical examination, pulse, blood pressure, respiratory rate, temperature will be recorded. A pre-medication of 100 mg of intravenous hydrocortisone injection and 45.5 mg intravenous or intramuscular pheniramine maleate injection will be administered within one hour prior to injection of **REGENACIP®**. You will be given a sedative injection prior to the procedure to help you relax and relieve the pain. **REGENACIP®** will then be injected in your calf muscle and around the ulcer. Monitoring of oxygen saturation will be done before the **REGENACIP®** administration and continued for 2 hours ±10 min after injection. You will be admitted in the hospital for 24 hours after **REGENACIP®** administration.

If you have any further questions on the use of this medicine, ask your doctor or surgeon.

1. **Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Hypersensitivity and mild pyrexia along with headache, muscle ache, nausea/vomiting, chills and shivering may be observed after the administration of the **REGENACIP®**. Pain and infection may be seen at the site of injection. The **REGENACIP®** contains a preservative dimethyl sulfoxide which can cause allergic reactions, such as skin rash, chest tightness or breathing problems. It may also cause bladder discomfort, garlic breath odor, garlic odor on the skin for as long as 72 hours after treatment.

1. **How to store REGENACIP®**

As this medicine will be used in the hospital, this medicine is directly supplied to the treating hospital / physician. The hospital staff is responsible for correct storage of the medicine before and during its use, as well as for its correct disposal.

1. **What REGENACIP® look like and content of the pack**

REGENACIP® is a cell suspension for injection. The cells are supplied in frozen condition in a cryobag and shipped in a cryoshipper at a temperature between – 185^0 C to – 196^0 C.

Before injection, the cryobag has to be thawed and mixed with 35 ml of Multiple Electrolyte Solution to make a final volume of 50 ml.

1. **Other information**
    a. **Use in Children and adolescents**

Do not give this medicine to children and adolescents (i.e. aged under 18 years) because the potential benefits and risks are unknown.

a. **Use in Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor/surgeon for advice before you are given this medicine. Treatment with **REGENACIP®** is not recommended during pregnancy or while breast-feeding. Women of childbearing age should use effective contraception during treatment with **REGENACIP®**.

a. **Driving and using machines**

REGENACIP® is not likely to affect your ability to drive or use tools or machines.

a. **Traceability**

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Details of Manufacturer

Stempeutics Research Pvt. Ltd. at 4th Floor,

Shirdi Sai Baba Cancer Hospital,

Manipal – 576 104, India.

Marketed By Cipla Ltd.

Registered Office:

Cipla House, Peninsula Business Park,

Ganpatrao Kadam Marg

Lower Parel

Mumbai – 400 013, India

Details of Permission or Licence Number with Date

Permission No. MF-121/ 2020 issued in Form CT-23; dated 07 Aug 2020 and amendment letter Ref. No. Stm-Cl/16/Stempeutics/20-BD; dated 03 Sep 2020 issued by CDSCO

Date of Revision

March 2021