SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Erythropoietin Injection B.P. (REPOITIN 2000)

Erythropoietin Injection B.P. (REPOITIN 4000)

Erythropoietin Injection B.P. (REPOITIN 5000)

Erythropoietin Injection B.P. (REPOITIN 10000)

Erythropoietin Injection B.P. (REPOITIN 40000)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

REPOITIN 2000 IU:

Each 0.5 mL contains: 2000 IU of Erythropoietin concentrated solution (Epoetin alfa) B.P.

REPOITIN 4000 IU:

Each 1.0 mL contains: 4000 IU of Erythropoietin concentrated solution (Epoetin alfa) B.P.

REPOITIN 5000 IU:

Each 0.5 mL contains: 5000 IU of Erythropoietin concentrated solution (Epoetin alfa) B.P.

REPOITIN 10000 IU:

Each 1.0 mL contains: 10000 IU of Erythropoietin concentrated solution (Epoetin alfa) B.P.

REPOITIN 40000 IU:

Each 1.0 mL contains: 40000 IU of Erythropoietin concentrated solution (Epoetin alfa) B.P.

Epoetin alfa is produced in CHO cell line by using recombinant DNA technology.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Injectable, Solution for Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of Anemia in Chronic Renal Failure patients
- Treatment of Chemotherapy induced Anemia in Cancer patients
- Treatment of Anemia in Zidovudine-treated HIV-infected patients
- Reduction of Allogenic Blood Transfusion in Surgery/Perisurgical Patients
- Increasing the yield of Preoperative Autologous Blood Donation in adult surgery patients

4.2 Posology and method of administration

Important: Use the lowest dose of REPOITIN that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need for RBC transfusion. REPOITIN should be administered under the supervision of a Registered Medical Practitioner only with dosage and route of administration decided by the RMP on a case to case basis based on current scientific and medical knowledge, and globally accepted practice guidelines.

Chronic Renal Failure Patients:

The recommended range for the starting dose of REPOITIN is 50-100 Units/kg, 2-3 times weekly for adult patients. The recommended starting dose for pediatric CRF patients on dialysis is 50 Units/kg TIW (thrice a week). The dose of REPOITIN should be reduced as the hemoglobin approaches 12 g/dL or increases by more than 1 g/dL in any 2-week period OR hematocrit approaches 30-33% or increase by more than 4 points in any 2-week period. Titrate dosing to achieve and maintain hemoglobin levels between 10-12 g/dL OR hematocrit between 30-33% (max 36%). REPOITIN may be given either as an i.v. or s.c. injection, though i.v. is the preferred and recommended route of administration in hemodialysis patients. In adult patients with CRF not on dialysis, REPOITIN may be given either as an i.v. or s.c. injection. During therapy, hematological parameters should be monitored regularly.

NOTE: It should be also noted that results from a large Multi-center, Randomized, Single-blind, Comparative Two-arm Phase III Pivotal Study for the treatment of Anemia in over 100 Indian CRF patients on maintenance hemodialysis, using a twice weekly dosing regimen also showed comparable increases in Hemoglobin and Hematocrit levels, reduction in RBC transfusions, as well as improvement in Quality of Life over a Correction Phase treatment duration of 12 weeks, with good safety and tolerability.

The decision of using REPOITIN either Thrice or Twice weekly rests with the Registered Medical Practitioner and can be made and therapy tailored on a case-to-case basis looking primarily at patient welfare, cost-benefit analysis, logistics and convenience. In line with international practice guidelines like NKF-DOQI and EBPG, REPOITIN should preferably be administered i.v. in all hemodialysis patients.

Pretherapy Iron Evaluation: Prior to and during REPOITIN therapy, the patient's iron stores, including transferrin saturation and serum ferritin, should be evaluated. Transferrin saturation should be at least 20%, and ferritin should be at least 100 ng/mL. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels that will adequately support erythropoiesis stimulated by REPOITIN.

Dose Adjustment: The dose should be adjusted for each patient to achieve and maintain a target hemoglobin not to exceed 12 g/dL. Increases in dose should not be made more frequently than once a month. If the hemoglobin is increasing and approaching 12 g/dL, the dose should be reduced by approximately 25 Units/kg TIW. If the hemoglobin continues to increase, dose should be temporarily withheld until the hemoglobin begins to decrease, at which point therapy should be reinitiated at a dose approximately 25% below the previous dose. If the hemoglobin increases by more

than 1 g/dL in a 2-week period, the dose should be decreased by approximately 25 Units/kg TIW. If the increase in the hemoglobin is less than 1 g/dL over 4 weeks and iron stores are adequate, the dose of REPOITIN may be increased by approximately

25 Units/kg TIW. Further increases may be made at 4-week intervals until the specified hemoglobin is obtained.

Maintenance Dose: The maintenance dose must be individualized for each patient on dialysis. In patients on hemodialysis, the median maintenance dose is normally reported to be 75 Units/kg TIW to maintain their hematocrit in the suggested target range, while in pediatric hemodialysis and adult peritoneal dialysis patients, the median maintenance dose has been reported as approximately 170 and 80 Units/kg/per week administered in divided doses (TIW or BIW) respectively to achieve the target range of 30% to 36%. In adult patients with CRF not on dialysis, the maintenance dose must also be individualized. REPOITIN doses of 75-150 Units/kg/week have been shown to maintain hematocrits of 36% to 38% for up to 6 months.

Lack or Loss of Response: Over 95% of patients with CRF respond with clinically significant increases in hematocrit, and virtually all patients are transfusion-independent within approximately 2 months of initiation of REPOITIN therapy. If the patient fails to respond or to maintain a response to doses within the recommended dosing range, the following etiologies should be considered and evaluated**:**

- Iron deficiency: Virtually all patients will eventually require supplemental iron
- Underlying infectious, inflammatory, or malignant processes.
- Occult blood loss.
- Underlying hematologic diseases (i.e., thalassemia, refractory anemia, or other Myelodysplastic disorders).
- Vitamin deficiencies: Folic acid or vitamin B12.
- Hemolysis.
- Aluminum intoxication.
- Osteitis fibrosa cystica.
- Pure Red Cell Aplasia (PRCA).

Cancer Patients on Chemotherapy:

Although no specific serum EPO level can be stipulated above which patients would be unlikely to respond to REPOITIN therapy, treatment of patients with grossly elevated serum EPO levels (e.g., > 200 mUnits/mL) is not generally recommended. Hemoglobin should be monitored on a weekly basis in patients receiving REPOITIN therapy until hemoglobin becomes stable, and dose of REPOITIN titrated to maintain

the desired hemoglobin target range of 10-12 g/dL. Two REPOITIN dosing regimens may be used in adults: (i) 150 Units/kg s.c. TIW (up to a maximum of 300 Units/kg s.c. TIW); or (ii) 40,000 Units s.c. weekly (up to a maximum of 60,000 Units s.c. weekly). If the hematocrit crosses 40%, withhold REPOITIN till it comes back under 36%, and then restart therapy at 25% lesser starting dose and titrate to maintain target hematocrit range. Dose of REPOITIN should also be reduced in case initial rise in hematocrit is too rapid (i.e. an increase of more than 2 percentage points in any one week period).

Zidovudine-treated HIV-infected Patients:

Prior to beginning REPOITIN it is generally recommended that the endogenous serum EPO level be determined (prior to transfusion). Available evidence suggests that patients receiving zidovudine with endogenous serum EPO levels > 500 mU/mL are unlikely to respond to therapy with rHuEPO. For adult patients with serum EPO levels ≤ 500 mU/mL who are receiving a dose of zidovudine ≤ 4200 mg/week, the recommended starting dose of REPOITIN is 100 Units/kg as an i.v. or s.c. injection TIW for 8 weeks with increase in 50-100 Units/kg increments TIW every 8 weeks depending on response up to a maximum of 300 Units/kg TIW. After attainment of the desired response (i.e., reduced transfusion requirements or increased hemoglobin), the dose of rHuEPO should be titrated to maintain the response based on factors such as variations in zidovudine dose and the presence of intercurrent infectious or inflammatory episodes. If the hematocrit crosses 40%, withhold REPOITIN till it comes back under 36%, and then restart therapy at 25% lesser starting dose and titrate to maintain target hematocrit range.

Perioperative Surgery Patients needing Allogenic Blood Transfusion:

Prior to initiating treatment with REPOITIN, a hemoglobin level should be obtained to establish that it is > 10 to ≤ 13 g/dL. The normally recommended dose of REPOITIN is 300 Units/kg/day s.c. for 10 days before surgery, on the day of surgery, and for 4 days after surgery. Another alternate dose schedule recommends 600 Units/kg REPOITIN subcutaneously in once weekly doses (21, 14, and 7 days before surgery) plus a fourth dose on the day of surgery. All patients should receive adequate iron

supplementation, which should be initiated no later than the beginning of treatment with REPOITIN and should continue throughout the course of therapy.

Adult Surgery Patients in an Autologous Pre-Donation Programme:

REPOITIN is indicated to facilitate autologous blood collection within a predeposit program and decrease the risk of receiving allogenic blood transfusions in adult surgery patients with hematocrits of 33-39%, and no iron deficiency, who are scheduled for major elective surgery and are expected to require more blood ($\geq$ 4 units for females; $\geq$ 5 units for males) than that which can be obtained through autologous blood collection techniques in the absence of REPOITIN or in the shorter than required time available. REPOITIN should be administered after the completion of each blood donation procedure. Iron status should be evaluated and iron deficiency, if present, corrected before enrolling patient into an autologous pre-donation programme and institution of REPOITIN therapy. All patients on REPOITIN therapy should be preferably placed on Iron supplementation (200 mg oral elemental iron daily) as soon as possible before the autologous predeposit in order to build up their iron stores, and should be kept on Iron supplementation throughout the course of REPOITIN therapy. Mildly anemic patients (hematocrit 33-39 vol% and/or hemoglobin 10-13 g/dL) requiring a predeposit of $\geq$ 4 units should receive 600 IU/kg twice weekly for three weeks prior to surgery, while non-anemic patients or those requiring less blood can be given 150-300 IU/kg twice weekly. The safety of pre- and perioperative use of REPOITIN has been studied only in patients who are receiving anticoagulant/ antithrombotic prophylaxis.

PREPARATION AND ADMINISTRATION OF REPOITIN

- Do not shake. Prolonged vigorous shaking may denature any glycoprotein, rendering it biologically inactive.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials exhibiting particulate matter or discoloration.
- Using aseptic techniques, attach a sterile needle to a sterile syringe. Remove the flip top from the vial and wipe the septum with a disinfectant. Insert the needle into the vial, and withdraw into the syringe an appropriate volume of solution.
- Vial contains no preservative. Use one dose per vial; do not re-enter the vial. Discard unused portions.

4.3 Contraindications

- Patients who develop pure red cell aplasia following treatment with REPOITIN should not receive any ESA
- Uncontrolled hypertension
- Known hypersensitivity to mammalian cell-derived products
- Known hypersensitivity to Albumin (Human) or any of the excipients / components used in the formulation
- Surgery patients who cannot receive antithrombotic prophylaxis

4.4 Special warnings and precautions for use

The parenteral administration of any biologic product should be attended by appropriate precautions in case allergic or other untoward reactions occur. The safety and efficacy of REPOITIN therapy have not been established in patients with a known history of a seizure disorder or underlying hematologic disease (e.g., sickle cell anemia, myelodysplastic syndromes, or hypercoagulable disorders).

Before starting the drug, check if patient has underlying high blood pressure, heart disease, any seizure disorder/epilepsy, or cancer. In such cases, patient may not be able to receive REPOITIN treatment, or may need treatment with lower doses and strict monitoring. In some female patients, menses have resumed following Erythropoietin therapy; the possibility of pregnancy should be discussed and the need for contraception evaluated.

Like all other Erythropoiesis-Stimulating Agents (ESAs), REPOITIN poses an increased risk of increased mortality, serious cardiovascular and thromboembolic events, and increased risk of tumor progression or recurrence when administered to achieve a hemoglobin level greater than 12 g/dL. Appropriate care should be taken while treating patients with REPOITIN. Special care should be taken to closely monitor and aggressively control blood pressure in patients treated with Erythropoietin. It is recommended that the dose of Erythropoietin be decreased if the hemoglobin increase exceeds 1 g/dL in any 2-week period, because of the possible association of excessive rate of rise of hemoglobin with an exacerbation of hypertension. While the relationship between seizures and the rate of rise of hemoglobin is uncertain, it is recommended that the dose of Erythropoietin be decreased if the hemoglobin increase exceeds 1 g/dL in any 2-week period.

Erythropoietin must be administered with caution in patients of CRF who are at risk of shunt thrombosis.

4.5 Interaction with other medicinal products and other forms of interaction:

There is no evidence of interaction of REPOITIN with other drugs observed in the course of clinical trials. However since cyclosporin is bound by red cells, there is potential for a drug interaction. If REPOITIN is given along with cyclosporin, blood levels of cyclosporin should be monitored and the dose of cyclosporin adjusted as the hematocrit rises. The effect of REPOITIN may be potentiated by the simultaneous administration of a haematinic agent, such as ferrous sulphate, when a deficiency state exists. Drugs that decrease erythropoiesis may decrease the response to REPOITIN. Animal experiments have been known to reveal that REPOITIN does not increase the myelotoxicity of cytostatic drugs like etoposide, cisplatin, cyclophosphamide, and fluorouracil.

4.6 Pregnancy and lactation:

There are no adequate and well-controlled studies in pregnant (Pregnancy Category C) women, but a potential risk appears to be minimal under therapeutic conditions. REPOITIN should be used during pregnancy only if potential benefit justifies the

potential risk to the fetus. It is not known whether REPOITIN is excreted in human milk. However, since many drugs are excreted in human milk, caution should be exercised when REPOITIN is administered to nursing women.

4.7 Effects on ability to drive and use machines:

While REPOITIN normally has no or negligible influence on the ability to drive and use machines, due to the rare but reported risk of seizures during the initial months of therapy, patients should be cautioned to avoid potentially hazardous activities such as driving or operating heavy machinery during that period.

4.8 Undesirable effects:

REPOITIN is generally well tolerated in humans, though as with other therapeutic proteins, immunogenic potential can be experienced rarely. A few cases of PRCA associated with antibodies with neutralizing activity have been reported in patients

receiving REPOITIN. Hypertension, Seizures, and Thromboembolic Events have been reported with REPOITIN usage. Shunt thomboses have also been known to occur.

a) Summary of Safety Profile:

In a large two-arm clinical trial conducted, REPOITIN was found to be safe and well tolerated. The non-serious adverse events observed were leucopenia (7.8%), thrombocytopenia (2.0%), chest pain (5.9%), abdominal pain (5.9%), oral toxicity (2.0%), toothache (2.0%), vomiting (3.9%), chills (7.8%), pyrexia (13.7%), AV fistula site hemorrhage (2.0%), graft complication (2.0%), increased AST (5.9%), ALT (5.9%), and hepatic enzyme (7.8%), reduced total lung capacity (2.0%), iron deficiency (2.0%), pain in back (2.0%), neck (2.0%), and extremity (2.0%), convulsions (3.9%), headache (3.9%), chest wall pain (2.0%), and cough (3.9%), nasopharyngitis (2.0%), and hypertension (3.9%).

None of the above adverse events reported were related to the study drug.

4.9 Overdose:

The therapeutic margin for REPOITIN is very wide, and even at very high serum levels no symptoms of poisoning have been observed. The maximum amount of REPOITIN that can be safely administered in single or multiple doses has not been

determined, though doses of up to 1500 Units/kg TIW for 3 to 4 weeks have reportedly been administered to adults without any direct toxic effects of REPOITIN itself. Therapy with REPOITIN can result in polycythemia if the hemoglobin is not carefully monitored and the dose appropriately adjusted. If the suggested target range is exceeded, REPOITIN may be temporarily withheld until the hemoglobin returns to the suggested target range; REPOITIN therapy may then be resumed using a lower dose. If polycythemia is of concern, phlebotomy may be indicated to decrease the hemoglobin.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Anti anemic, ATC code: B03XA01

Mechanism of Action:

REPOITIN mainly controls and stimulates the late stages of red blood cell production. REPOITIN regulates the proliferation, survival and differentiation of committed erythroid precursor cells. It increases bone marrow erythroid activity and stimulates red blood cell production by stimulating the division and differentiation of committed erythroid progenitors in the bone marrow. REPOITIN also accelerates the release of reticulocytes without alteration of either the cell cycle or the number of mitotic divisions in the differentiation process. It also increases the number of developing erythroid precursors in the bone marrow, followed by the increase in red cell counts, hemoglobin and hematocrit.

5.2 Pharmacokinetic properties:

The elimination half-life of REPOITIN following i.v. administration in healthy individuals and in patients with CRF reportedly appears to range from 4-16 hours. In patients with impaired renal function the half-life is prolonged relative to those with normal renal function. Peak serum levels are reportedly achieved within 4-24 hours following s.c. administration of usual therapeutic doses with serum erythropoietin

levels remaining above baseline for 2-4 days, while following i.v. dosing with usual therapeutic doses, erythropoietin levels reportedly decline to base levels in 1-3 days. Because of its protein nature, REPOITIN is destroyed in GI tract and must be administered parenterally (i.v. or s.c.). While serum concentrations peak sooner and are substantially higher with i.v. than s.c. route, they are less sustained, and the i.v. route offers no clinical advantage over the s.c. route except in patients with ready available vascular access. With usual i.v. or s.c. dosing, detectable serum concentrations of erythropoietin are reportedly maintained for at least 24 hours. Bioavailability is lower but its half-life is longer after s.c. than after i.v. administration..

5.3 Preclinical safety data

While teratogenecity, mutagenecity, and carcinogenicity studies were not done, REPOITIN was tested more than adequately in animal studies involving a total of four acute single dose studies and two repeat dose 28-day toxicity studies conducted in rats and rabbits. In each of these studies, REPOITIN was diluted with phosphate buffer and administered either intravenously or subcutaneously. The above all inclusive toxicity

studies in rats and rabbits clearly showed that REPOITIN did not produce any local intolerance or systemic toxicity at 200 times (6600 IU/kg) the estimated human dose in acute studies in rats and rabbits by the intravenous or subcutaneous routes and at 100 times (3300 IU/kg) estimated human dose by the subcutaneous route in rats and rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Human Albumin

Sodium Chloride

Sodium Phosphate

Sodium Dihydrogen Phosphate monohydrate

Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Vial: 24 months (2 years)

6.4 Special precautions for storage

Store at 2°C to 8°C. The cold chain should be closely maintained until administration to the patient. Do not freeze or shake, and protect from light.

6.5 Nature and contents of Container

2000 IU/0.5 mL:

0.5 mL of clear solution for injection in a type-1 glass vial with bromobutyl rubber stopper and aluminium seal having flip off cap.

Each Pack contains 1 or 6 vials (Not all pack sizes may be marketed).

4000 IU/1.0 mL:

1.0 mL of clear solution for injection in a type-1 glass vial with bromobutyl rubber

stopper and aluminium seal having flip off cap.

Each Pack contains 1 or 6 vials (Not all pack sizes may be marketed).

5000 IU/0.5 mL:

0.5 mL of clear solution for injection in a type-1 glass vial with bromobutyl rubber stopper and aluminium seal having flip off cap.

Each Pack contains 1 or 6 vials (Not all pack sizes may be marketed).

6000 IU/0.6 mL:

0.5 mL of clear solution for injection in a type-1 glass vial with bromobutyl rubber stopper and aluminium seal having flip off cap.

Each Pack contains 1 or 6 vials (Not all pack sizes may be marketed).

10000 IU/ mL:

1 mL of clear solution for injection in a type-1 glass vial with bromobutyl rubber stopper and aluminium seal having flip off cap.

Each Pack contains 1 or 6 vials (Not all pack sizes may be marketed).

40000 IU/ mL:

1 mL of clear solution for injection in a type-1 glass vial with bromobutyl rubber stopper and aluminium seal having flip off cap.

Each Pack contains 1 or 6 vials (Not all pack sizes may be marketed).

6.6 Special precautions for disposal and other handling:

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials exhibiting particulate matter or discoloration.
- Using aseptic techniques, attach a sterile needle to a sterile syringe. Remove the flip top from the vial and wipe the septum with a disinfectant. Insert the needle into the vial, and withdraw into the syringe an appropriate volume of solution.
- Do not Shake
- This product is for single use only. Discard unused medicine.
- Repoitin should not be used if the solution has been frozen, even if accidentally.
- Do not administer by intravenous infusion or in conjunction with other drug solutions.

- Any unused product or waste material should be disposed of in accordance with local regulatory requirements.

7. MARKETING AUTHORISATION HOLDER

SERUM INSTITUTE OF INDIA PVT. LTD.

212/2, Hadapsar, Pune 411028, India

8. MARKETING AUTHORISATION NUMBER(S)

SER/IND/017

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorization: 03rd September 2015

Date of latest renewal: 24th July 2021

10. DATE OF REVISION OF THE TEXT

July 2023