SUMMARY OF PRODUCT CHARACTERISTICS

1.0 Name of the Medicinal Product

Darbepoetin alfa Injection.

2.0 Qualitative and Quantitative Composition

Darbepoetin alfa in pre-filled syringes is a sterile, clear, colorless and preservative-free solution, available in different dose strengths.

Darbepoetin 10 micrograms solution for injection in pre-filled syringe

Each pre-filled syringe contains 10 micrograms of darbepoetin alfa in 0.40 mL (25 mcg/mL).

Darbepoetin 15 micrograms solution for injection in pre-filled syringe
Each pre-filled syringe contains 15 micrograms of darbepoetin alfa in 0.375 mL (40 mcg/mL).

Darbepoetin 20 micrograms solution for injection in pre-filled syringe
Each pre-filled syringe contains 20 micrograms of darbepoetin alfa in 0.50 mL (40 mcg/mL).

Darbepoetin 25 micrograms solution for injection in pre-filled syringe
Each pre-filled syringe contains 25 micrograms of darbepoetin alfa in 0.42 mL (60 mcg/mL).

Darbepoetin 40 micrograms solution for injection in pre-filled syringe
Each pre-filled syringe contains 40 micrograms of darbepoetin alfa in 0.40 mL (100 mcg/mL).

Darbepoetin 60 micrograms solution for injection in pre-filled syringe
Each pre-filled syringe contains 60 micrograms of darbepoetin alfa in 0.30 mL (200 mcg/mL).

Darbepoetin 100 micrograms solution for injection in pre-filled syringe
Each pre-filled syringe contains 100 micrograms of darbepoetin alfa in 0.50 mL (200 mcg/mL).

Darbepoetin 150 micrograms solution for injection in pre-filled syringe
Each pre-filled syringe contains 150 micrograms of darbepoetin alfa in 0.30 mL (500 mcg/mL).

Darbepoetin 200 micrograms solution for injection in pre-filled syringe
Each pre-filled syringe contains 200 micrograms of darbepoetin alfa in 0.40 mL (500 mcg/mL).

Darbepoetin 300 micrograms solution for injection in pre-filled syringe
Each pre-filled syringe contains 300 micrograms of darbepoetin alfa in 0.60 mL (500 mcg/mL).

Darbepoetin 500 micrograms solution for injection in pre-filled syringe
Each pre-filled syringe contains 500 micrograms of darbepoetin alfa in 1.0 mL (500 mcg/mL). Darbepoetin alfa is produced by gene-technology in Chinese Hamster Ovary Cells (CHO-K1). For dilution and other handling recommendations, see section 6.6.

For full list of Excipients, see section 6.1

3.0 Pharmaceutical Form

Darbepoetin alfa is a clear, colourless solution.

Darbepoetin Solution for injection in Single-dose pre-filled syringe (PFS) for subcutaneous or intravenous use.
Darbepoetin alfa drug product having the following dose strengths: 10mcg/0.4mL, 15mcg/0.375mL, 20mcg/0.5mL, 25mcg/0.42mL, 40mcg/0.4mL, 60mcg/0.3mL, 100mcg/0.5mL, 150mcg/0.3mL, 200mcg/0.4mL, 300mcg/0.6mL and 500mcg/1mL.

4.0 Clinical Particulars

4.1 Therapeutic indications

Darbepoetin alfa injection is indicated for the

- treatment of Anemia with chronic renal failure including patients on dialysis and patients not on dialysis.
- treatment of symptomatic anemiain adult cancer patients with non-myeloid malignancies receiving chemotherapy.

4.2 Posology and method of administration

Treatment of symptomatic anaemia in adult chronic renal failure patients

Anaemia symptoms and sequelae may vary with age, gender, and overall burden of disease; a physician's evaluation of the individual patient's clinical course and condition is necessary. Darbepoetin alfa should be administered either subcutaneously or intravenously in order to increase haemoglobin to not greater than 12 g/dL (7.5 mmol/L). Subcutaneous use is preferable in patients who are not receiving haemodialysis to avoid the puncture of peripheral veins.

Patients should be monitored closely to ensure that the lowest approved effective dose of Darbepoetin alfa is used to provide adequate control of the symptoms of anaemia whilst maintaining a haemoglobin concentration below or at 12 g/dL (7.5 mmol/L). Caution should be exercised with escalation of Darbepoetin alfa doses in patients with chronic renal failure. In patients with a poor haemoglobin response to Darbepoetin alfa, alternative explanations for the poor response should be considered.

Due to intra-patient variability, occasional individual haemoglobin values for a patient above and below the desired haemoglobin level may be observed. Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin target range of

10 g/dL (6.2 mmol/L) to 12 g/dL (7.5 mmol/L). A sustained haemoglobin level of greater than 12 g/dL (7.5 mmol/L) should be avoided; guidance for appropriate dose adjustment for when haemoglobin values exceeding 12 g/dL (7.5 mmol/L) are observed are described below. A rise in haemoglobin of greater than 2 g/dL (1.25 mmol/L) over a four-week period should be avoided. If it occurs, appropriate dose adjustment should be made as provided.

Treatment with Darbepoetin alfa is divided into two stages, correction and maintenance phase. Guidance is given separately for adult and paediatric patients.

Adult patients with chronic renal failure

Correction phase:

The initial dose by subcutaneous or intravenous administration is 0.45 mcg/kg body weight, as a single injection once weekly. Alternatively, in patients not on dialysis, the following initial doses can also be administered subcutaneously as a single injection: 0.75 mcg/kg once every two weeks or 1.5 mcg/kg once monthly. If the increase in haemoglobin is inadequate (less than 1 g/dL (0.6 mmol/L) in four weeks) increase the dose by approximately 25%. Dose increases must not be made more frequently than once every four weeks.

If the rise in haemoglobin is greater than 2 g/dL (1.25 mmol/L) in four weeks reduce the dose by approximately 25%. If the haemoglobin exceeds 12 g/dL (7.5 mmol/L), a dose reduction should be considered. If the haemoglobin continues to increase, the dose should be reduced by approximately 25%. If after a dose reduction, haemoglobin continues to increase, the dose should be temporarily withheld until the haemoglobin begins to decrease, at which point therapy should be reinitiated at approximately 25% lower than the previous dose.

The haemoglobin should be measured every one or two weeks until it is stable. Thereafter the haemoglobin can be measured at longer intervals.

Maintenance phase:

In dialysis patients, Darbepoetin alfa may continue to be administered as a single injection once weekly or once every two weeks. Dialysis patients converting from once weekly to once every other week dosing with Darbepoetin alfa should initially receive a dose equivalent to twice the previous once weekly dose.

In patients not on dialysis, Darbepoetin alfa may continue to be administered as a single injection once weekly or once every two weeks or once monthly. For patients treated with

Darbepoetin alfa once every two weeks, after the target haemoglobin has been achieved, Darbepoetin alfa may then be administered subcutaneously once monthly using an initial dose equal to twice the previous once every two-week dose.

Dosing should be titrated as necessary to maintain the haemoglobin target.

If a dose adjustment is required to maintain haemoglobin at the desired level, it is recommended that the dose is adjusted by approximately 25%.

If the rise in haemoglobin is greater than 2 g/dL (1.25 mmol/L) in four weeks reduce the dose by approximately 25%, depending on the rate of increase. If the haemoglobin exceeds 12 g/dL (7.5 mmol/L), a dose reduction should be considered. If the haemoglobin continues to increase, the dose should be reduced by approximately 25%. If after a dose reduction, haemoglobin continues to increase, the dose should be temporarily withheld until the haemoglobin begins to decrease, at which point therapy should be reinitiated at approximately 25% lower than the previous dose.

After any dose or schedule adjustment the haemoglobin should be monitored every one or two weeks. Dose changes in the maintenance phase of treatment should not be made more frequently than every two weeks.

When changing the route of administration, the same dose must be used and the haemoglobin monitored every one or two weeks so that the appropriate dose adjustments can be made to keep the haemoglobin at the desired level.

Clinical studies have demonstrated that adult patients receiving r-HuEPO one, two or three times weekly may be converted to once weekly or once every other week Darbepoetin alfa. The initial weekly dose of Darbepoetin alfa (mcg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 200. The initial every other week dose of Darbepoetin alfa (mcg/every other week) can be determined by dividing the total cumulative dose of r- HuEPO administered over a two-week period by 200. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Darbepoetin alfa for r-HuEPO the haemoglobin should be monitored every one or two weeks and the same route of administration should be used.

Treatment of symptomatic chemotherapy-induced anaemia in cancer patients

Darbepoetin alfa should be administered by the subcutaneous route to patients with anaemia (e.g. haemoglobin concentration ≤ 10 g/dL (6.2 mmol/L)) in order to increase haemoglobin to not greater than 12 g/dL (7.5 mmol/L). Anaemia symptoms and sequelae may vary with age, gender, and overall burden of disease; a physician's evaluation of the individual patient's clinical course and condition is necessary.

Due to intra-patient variability, occasional individual haemoglobin values for a patient above and below the desired haemoglobin level may be observed. Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin target range of 10 g/dL (6.2 mmol/L) to 12 g/dL (7.5 mmol/L). A sustained haemoglobin level of greater than 12 g/dL (7.5 mmol/L) should be avoided; guidance for appropriate dose adjustments for when haemoglobin values exceeding 12 g/dL (7.5 mmol/L) are observed are described below.

The recommended initial dose is 500 mcg (6.75 mcg/kg) given once every three weeks, or once weekly dosing can be given at 2.25 mcg/kg body weight. If the clinical response of the patient (fatigue, haemoglobin response) is inadequate after nine weeks, further therapy may not be effective.

Darbepoetin alfa therapy should be discontinued approximately four weeks after the end of chemotherapy.

Once the therapeutic objective for an individual patient has been achieved, the dose should be reduced by 25 to 50% in order to ensure that the lowest approved dose of Darbepoetin alfa is used to maintain haemoglobin at a level that controls the symptoms of anaemia. Appropriate dose titration between 500 mcg, 300 mcg, and 150 mcg should be considered.

Patients should be monitored closely, if the haemoglobin exceeds 12 g/dL (7.5 mmol/L), the dose should be reduced by approximately 25 to 50%. Treatment with Darbepoetin alfa should be temporarily discontinued if haemoglobin levels exceed 13 g/dL (8.1 mmol/L). Therapy should be reinitiated at approximately 25% lower than the previous dose after haemoglobin levels fall to 12 g/dL (7.5 mmol/L) or below.

If the rise in haemoglobin is greater than 2 g/dL (1.25 mmol/L) in 4 weeks, the dose should be reduced by 25 to 50%.

<u>Method of administration</u>

Darbepoetin alfa may be administered subcutaneously by the patient or a carer after being trained by a doctor, nurse or pharmacist.

Darbepoetin alfa 10, 15, 20, 25, 40, 50, 60, 100, 150, 300, 500 micrograms solution for injection in pre-filled syringe

Darbepoetin alfa is administered either subcutaneously or intravenously as described in the posology.

Rotate the injection sites and inject slowly to avoid discomfort at the site of injection. Darbepoetin alfa is supplied ready for use in a pre-filled syringe. The instructions for use, handling and disposal are given in section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

In order to improve the traceability of erythropoiesis-stimulating agents (ESAs), the trade name of the administered ESA should be clearly recorded (or stated) in the patient file.

Blood pressure should be monitored in all patients, particularly during initiation of Darbepoetin alfa therapy. If blood pressure is difficult to control by initiation of appropriate measures, the haemoglobin may be reduced by decreasing or withholding the dose of Darbepoetin alfa (see section 4.2). Cases of severe hypertension, including hypertensive crisis, hypertensive encephalopathy, and seizures, have been observed in CRF patients treated with Darbepoetin alfa.

In order to ensure effective erythropoiesis, iron status should be evaluated for all patients prior to and during treatment and supplementary iron therapy may be necessary.

Non-response to therapy with Darbepoetin alfa should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of ESAs and should therefore be corrected. Intercurrent infections, inflammatory or traumatic episodes, occult blood loss, haemolysis, severe aluminium toxicity, underlying haematologic diseases, or bone marrow fibrosis may also compromise the erythropoietic response. A reticulocyte count should

be considered as part of the evaluation. If typical causes of non-response are excluded, and the patient has reticulocytopenia, an examination of the bone marrow should be considered. If the bone marrow is consistent with PRCA, testing for anti-erythropoietin antibodies should be performed.

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported in association with epoetin treatment. More severe cases have been observed with long-acting epoetins.

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, Darbepoetin alfa should be withdrawn immediately and an alternative treatment considered. If the patient has developed a severe cutaneous skin reaction such as SJS or TEN due to the use of Darbepoetin alfa, treatment with Darbepoetin alfa must not be restarted in this patient at any time.

Pure red cell aplasia caused by neutralising anti-erythropoietin antibodies has been reported in association with ESAs, including Darbepoetin alfa. This has been predominantly reported in patients with CRF treated subcutaneously. These antibodies have been shown to cross-react with all erythropoietic proteins, and patients suspected or confirmed to have neutralising antibodies to erythropoietin should not be switched to Darbepoetin alfa (see section 4.8).

A paradoxical decrease in haemoglobin and development of severe anaemia associated with low reticulocyte counts should prompt to discontinue treatment with epoetin and perform anti- erythropoietin antibody testing. Cases have been reported in patients with hepatitis C treated with interferon and ribavirin, when epoetins are used concomitantly. Epoetins are not approved in the management of anaemia associated with hepatitis C.

Active liver disease was an exclusion criterion in all studies of Darbepoetin alfa, therefore no data are available from patients with impaired liver function. Since the liver is thought to be the principal route of elimination of darbepoetin alfa and r-HuEPO, Darbepoetin alfa should be used with caution in patients with liver disease. Darbepoetin alfa should also be used with caution in those patients with sickle cell anaemia.

Misuse of Darbepoetin alfa by healthy persons may lead to an excessive increase in packed cell volume. This may be associated with life-threatening complications of the cardiovascular system.

The needle cap of the pre-filled syringe or pre-filled pen contains dry natural rubber (a derivative of latex), which may cause allergic reactions.

Darbepoetin alfa should be used with caution in patients with epilepsy. Convulsions have been reported in patients receiving Darbepoetin alfa.

The reported risk of thrombotic vascular events (TVEs) should be carefully weighed against the benefits to be derived from treatment with darbepoetin alfa particularly in patients with pre- existing risk factors for TVE, including obesity and prior history of TVEs (e.g., deep venous thrombosis, pulmonary embolism, and cerebral vascular accident).

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

Chronic renal failure patients

In patients with chronic renal failure, maintenance haemoglobin concentration should not exceed the upper limit of the target haemoglobin concentration recommended in section 4.2. In clinical studies, an increased risk of death, serious cardiovascular or cerebrovascular events including stroke, and vascular access thrombosis was observed when ESAs were administered to target a haemoglobin of greater than 12 g/dL (7.5 mmol/L).

Caution should be exercised with escalation of Darbepoetin alfa doses in patients with chronic renal failure, since high cumulative epoetin doses may be associated with an increased risk of mortality, serious cardiovascular and cerebrovascular events. In patients with a poor haemoglobin response to epoetins, alternative explanations for the poor response should be considered.

Controlled clinical trials have not shown significant benefits attributable to the administration of epoetins when haemoglobin concentration is increased beyond the level necessary to control symptoms of anaemia and to avoid blood transfusion.

Supplementary iron therapy is recommended for all patients with serum ferritin values below 100 mcg/L or whose transferrin saturation is below 20%.

Serum potassium levels should be monitored regularly during Darbepoetin alfa therapy. Potassium elevation has been reported in a few patients receiving Darbepoetin alfa, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Darbepoetin alfa administration until the level has been corrected.

Cancer patients

Effect on tumour growth

Epoetins are growth factors that primarily stimulate red blood cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumour cells. As with all growth factors, there is a concern that epoetins could stimulate the growth of tumours. In several controlled studies, epoetins have not been shown to improve overall survival or decrease the risk of tumour progression in patients with anaemia associated with cancer.

In controlled clinical studies, use of Darbepoetin alfa and other ESAs have shown:

• shortened time to tumour progression in patients with advanced head and neck cancer receiving radiation therapy when administered to target a haemoglobin of greater than 14 g/dL (8.7 mmol/L), ESAs are not indicated for use in this patient population.

• shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to target a haemoglobin of 12-14 g/dL (7.5-8.7 mmol/L).

• increased risk of death when administered to target a haemoglobin of 12 g/dL (7.5 mmol/L) in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated for use in this patient population.

• an observed 9% increase in risk for PD or death in the epoetin alfa plus SOC group from a primary analysis and a 15% increased risk that cannot be statistically ruled out in patients with metastatic breast cancer receiving chemotherapy when administered to achieve a haemoglobin concentration range of 10 to 12 g/dL (6.2 to 7.5 mmol/L).

• non-inferiority of darbepoetin alfa to placebo for overall survival and progression free survival in patients with advanced stage non-small cell lung cancer receiving chemotherapy when administered to a target haemoglobin of 12 g/dL (7.5 mmol/L) (see section 5.1).

In view of the above, in some clinical situations blood transfusion should be the preferred treatment for the management of anaemia in patients with cancer. The decision to administer recombinant erythropoietins should be based on a benefit-risk assessment with the participation of the individual patient, which should take into account the specific clinical context. Factors that should be considered in this assessment should include the type of tumour and its stage; the degree of anaemia; life-expectancy; the environment in which the patient is being treated; and patient preference (see section 5.1).

In patients with solid tumours or lymphoproliferative malignancies, if the haemoglobin value exceeds 12 g/dL (7.5 mmol/L), the dosage adaptation described in section 4.2 should be closely respected, in order to minimise the potential risk of thromboembolic events. Platelet counts and haemoglobin level should also be monitored at regular intervals.

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies of Darbepoetin alfa have been performed.

The clinical results obtained so far do not indicate any interaction of Darbepoetin alfa with other substances. However, there is potential for an interaction with substances that are highly bound to red blood cells e.g. Cyclosporin, Tacrolimus. If Darbepoetin alfa is given concomitantly with any of these treatments, blood levels of these substances should be monitored and the dosage adjusted as the haemoglobin rises.

4.6 Pregnancy and lactation Pregnancy

Pregnancy Category C:

There are no adequate and well-controlled studies in pregnant women.
Darbepoetin alfa should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Breast-feeding

It is not known whether Darbepoetin alfa is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Darbepoetin alfa is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

Darbepoetin alfa has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

As described in detail in section "Warnings & Precautions" following serious adverse reactions

have been reported with Darbepoetin Alfa:

- Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism
- Increased mortality and/or increased risk of tumor progression or recurrence in Patients With Cancer
- Severe Cutaneous Reactions: Stevens-Johnson syndrome and toxic epidermal necrolysis
- Hypertension
- Seizures
- PRCA
- Serious allergic reactions

Immunogenicity

There is a potential for immunogenicity with Darbepoetin alfa like all therapeutic proteins. Neutralizing antibodies to Darbepoetin alfa that cross-react with endogenous erythropoietin and other ESAs can result in PRCA or severe anemia (with or without other cytopenia.

***Chronic Renal* Failure**

Patients Adult Patients

Adverse reactions occurring in patients treated with Darbepoetin alfa are: Hypertension, dyspnea, peripheral edema, cough, procedural hypotension, angina pectoris, vascular access complications, fluid overload, rash/erythema and arteriovenous graft thrombosis.

Pediatric Patients

The most frequently reported serious adverse reactions with Darbepoetin alfa in clinical trials were hypertension and convulsions. The most commonly reported adverse reactions were hypertension, injection site pain, rash, and convulsions. Studies have not evaluated the effects of Darbepoetin alfa when administered to pediatric patients as the initial treatment for the anemia associated with CKD.

Cancer Patients Receiving Chemotherapy

The adverse reactions from controlled clinical studies and post-marketing experience are hypersensitivity, convulsions, hypertension, thromboembolic events, including pulmonary embolism, myocardial infarction, cerebrovascular disorders encompasses CNS hemorrhages and cerebrovascular accidents (ischemic and hemorrhagic), rash/erythema, Oedema and injection site pain.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

The maximum amount of Darbepoetin alfa that can be safely administered in single or multiple doses has not been determined. Therapy with Darbepoetin alfa can result in polycythaemia if the haemoglobin is not carefully monitored and the dose appropriately adjusted. Cases of severe hypertension have been observed following overdose with Darbepoetin alfa.
In the event of polycythaemia, Darbepoetin alfa should be temporarily withheld. If clinically indicated, phlebotomy may be performed.

5.0 Pharmacological Properties

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Anti-anaemic preparations, other antianemic preparations,

ATC Code: B03XA02.

Mechanism of Action

Human erythropoietin is an endogenous glycoprotein hormone that is the primary regulator of erythropoiesis through specific interaction with the erythropoietin receptor on the erythroid progenitor cells in the bone marrow. The production of erythropoietin primarily occurs in and is regulated by the kidney in response to changes in tissue oxygenation. Production of endogenous erythropoietin is impaired in patients with chronic renal failure and the primary cause of their anemia is due to erythropoietin deficiency. In patients with cancer receiving chemotherapy the etiology of anemia is multifactorial. In these patients, erythropoietin deficiency and a reduced response of erythroid progenitor cells to endogenous erythropoietin both contribute significantly towards their anemia.

Pharmacodynamics

Darbepoetin alfa stimulates erythropoiesis by the same mechanism as the endogenous hormone. Darbepoetin alfa has five N-linked carbohydrate chains whereas the endogenous hormone and recombinant human erythropoietins (r-HuEPO) have three. The additional sugar residues are molecularly indistinct from those on the endogenous hormone. Due to its increased carbohydrate content Darbepoetin alfa has a longer terminal half-life than r-HuEPO and consequently a greater in vivo activity. Despite these molecular changes, Darbepoetin alfa retains a very narrow specificity for the erythropoietin receptor. Increased hemoglobin levels are not generally observed until 2 to 6 weeks after initiating treatment with Darbepoetin alfa.

5.2 Pharmacokinetic properties

Due to its increased carbohydrate content the level of darbepoetin alfa in the circulation remains above the minimum stimulatory concentration for erythropoiesis for longer than the equivalent molar dose of r-HuEPO, allowing darbepoetin alfa to be administered less frequently to achieve the same biological response.

Chronic renal failure patients

The pharmacokinetics of darbepoetin alfa has been studied clinically in chronic renal failure patients following intravenous and subcutaneous administration. The terminal half-life of darbepoetin alfa is 21 hours (SD 7.5) when administered intravenously. Clearance of darbepoetin alfa is 1.9 mL/hr/kg (SD 0.56) and the volume of distribution (Vss) is approximately equal to plasma volume (50 mL/kg). Bioavailability is 37% with subcutaneous administration. Following monthly administration of darbepoetin alfa, at subcutaneous doses ranging from 0.6 to 2.1 mcg/kg, the terminal half-life was 73 hours (SD 24). The longer terminal half-life of darbepoetin alfa administered subcutaneously compared to intravenously is due to subcutaneous absorption kinetics. In clinical studies, minimal accumulation was observed with either route of administration. In preclinical studies it has been shown that renal clearance is minimal (up to 2% of total clearance), and does not affect the serum half-life.

Data from 809 patients receiving Aranesp in European clinical studies were analysed to assess the dose required to maintain haemoglobin; no difference was observed between the average weekly dose administered via the intravenous or subcutaneous routes of injection.

The pharmacokinetics of darbepoetin alfa in paediatric patients (2 to 16 years) with CRF who were either receiving or not receiving dialysis was assessed for sampling periods up to 2 weeks (336 hours) after one or two subcutaneous or intravenous doses. Where the same sampling duration was used, observed pharmacokinetic data and population pharmacokinetic modelling demonstrated that the pharmacokinetics of darbepoetin alfa was similar for paediatric and adult patients with CRF.

In a phase 1 pharmacokinetic study, following intravenous administration, an approximate 25% difference between paediatric and adult patients in the area under the curve from time 0 to infinity (AUC[0-∞]) was observed; however, this difference was less than the 2-fold range in AUC(0-∞) observed for the paediatric patients. AUC(0-∞) was similar between adult and

paediatric patients with CRF following subcutaneous administration. Half-life was also similar between adult and paediatric patients with CRF following both intravenous and subcutaneous administration.

Cancer patients receiving chemotherapy

Following subcutaneous administration of 2.25 µg/kg to adult cancer patients a mean peak concentration of 10.6 ng/ml (SD 5.9) of darbepoetin alfa was reached at a mean time of 91 hours (SD 19.7). These parameters were consistent with dose linear pharmacokinetics over a wide dose range (0.5 to 8 µg/kg weekly and 3 to 9 µg/kg every two weeks). Pharmacokinetic parameters did not change on multiple dosing over 12 weeks (dosing every week or every two weeks). There was an expected moderate (< 2 fold) increase in serum concentration as steady state was approached, but no unexpected accumulation upon repeated administration. A pharmacokinetic study in patients with chemotherapy-induced anemia treated with 6.75 µg/kg darbepoetin alfa administered SC every 3 weeks in combination with chemotherapy was conducted which allowed for full characterisation of the terminal half-life. In this study, mean (SD) terminal half- life was 74 (SD 27) hours.

5.3 Preclinical safety data

In single dose toxicity studies with Darbepoetin alfa in rats and mice, no clinical signs of toxicity and mortality were observed at doses of 258.23µg/kg and 512.30µg/kg respectively. In repeated dose toxicity studies with Darbepoetin alfa in rats and rabbits, the no observed adverse effect level (NOAEL) were observed at doses of 258.23µg/kg and 129.12µg/kg respectively. Darbepoetin alfa was also found to produce marked increases in haemoglobin, haematocrits, red blood cell counts and reticulocytes, which correspond to the expected pharmacological effects. In guinea pigs, Darbepoetin alfa was observed to have no skin sensitization potential. These observations were observed with studies involving in-house Darbepoetin alfa product.

Adverse events at very high doses of Darbepoetin alfa are all considered to be related to an exaggerated pharmacological effect (decreased tissue perfusion due to increased blood viscosity). These include myelofibrosis and splenic hypertrophy as well as broadening of the ECG-QRS complex, without significant dysrhythmia or any effect on the QT interval. These observations were found in published studies involving dogs.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Darbepoetin alfa was not mutagenic or clastogenic under the conditions tested. Darbepoetin alfa was negative in the in vitro bacterial

reverse mutation assay, the in vitro mammalian cell gene mutation assay (using CHO cells), and in the in vivo mouse erythrocyte micronucleus assay. Darbepoetin alfa has neither been found to have any genotoxic potential nor any effect on the proliferation of non-haematological cells in vitro or in vivo in published studies. In the chronic toxicity studies no tumourigenic or unexpected mitogenic responses are observed in any tissue type. The carcinogenic potential of Darbepoetin alfa has not been evaluated in long-term animal studies. These observations were found in published studies.

Reproductive Toxicology Studies: In rats and rabbits, no clinically relevant evidence of harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development have been observed in the published studies. In these studies, placental transfer was found to be minimal and no alteration of fertility had been detected. These observations were found in published studies.

6.0 Pharmaceutical Particulars

6.1 List of excipients

S. No.	Ingredients	10mcg / 0.4mL	15mcg/ 0.375mL	20mcg / 0.5mL	25mcg / 0.42ml	40mcg /0.4ml	60mcg / 0.3ml
1	Sodium phosphate monobasic monohydrate	0.85 mg	0.80 mg	1.06 mg	0.89 mg	0.85 mg	0.64 mg
2	Sodium phosphate dibasic anhydrous	0.26 mg	0.25 mg	0.33 mg	0.28 mg	0.26 mg	0.20 mg
3	Sodium chloride	3.27 mg	3.07 mg	4.09 mg	3.44 mg	3.27 mg	2.45 mg
4	Polysorbate 80	0.020 mg	0.018 mg	0.025 mg	0.021 mg	0.020 mg	0.015 mg
5	Water for Injection	q.s. to 0.4 ml	q.s. to 0.375 ml	q.s. to 0.5 ml	q.s. to 0.42 ml	q.s. to 0.4 ml	q.s. to 0.3 ml

S. No.	Ingredients	100mcg /0.5ml	150mcg /0.3ml	200mcg /0.4ml	300mcg /0.6ml	500mcg /1.0ml
1	Sodium phosphate monobasic monohydrate	1.06 mg	0.64 mg	0.85 mg	1.27 mg	2.12 mg
2	Sodium phosphate dibasic anhydrous	0.33 mg	0.20 mg	0.26 mg	0.40 mg	0.66 mg
3	Sodium chloride	4.09 mg	2.45 mg	3.27 mg	4.91 mg	8.18 mg
4	Polysorbate 80	0.025 mg	0.015 mg	0.020 mg	0.03 mg	0.05 mg

5	Water for Injection	q.s. to 0.5 ml	q.s. to 0.3 ml	q.s. to 0.4 ml	q.s. to 0.6 ml	q.s. to 1.0 ml

pH 6.2 ± 0.2

6.2 Incompatibilities

Do not administer Darbepoetin alfa injection in conjunction with other drug solutions.

6.3 Shelf life

36 months from the date of manufacture.

6.4 Special precautions for storage

Store at 2°C to 8°C. Do not freeze or shake. Protect from light. Keep out of reach of children.

6.5 Nature and contents of container

The following presentations are available:

1	**Darbepoetin alfa injection: 10 mcg** Each 0.40 ml single dose prefilled syringe contains: Darbepoetin alfa (r-DNA origin) 10 mcg
2	**Darbepoetin alfa injection: 15 mcg** Each 0.375 ml single dose prefilled syringe contains: Darbepoetin alfa (r-DNA origin) 15 mcg
3	**Darbepoetin alfa injection: 20 mcg** Each 0.50 ml single dose prefilled syringe contains: Darbepoetin alfa (r-DNA origin) 20 mcg
4	**Darbepoetin alfa injection: 25 mcg** Each 0.42 ml single dose prefilled syringe contains: Darbepoetin alfa (r-DNA origin) 25 mcg
5	**Darbepoetin alfa injection: 40 mcg**

	Each 0.40 ml single dose prefilled syringe contains: Darbepoetin alfa (r-DNA origin) 40 mcg
6	**Darbepoetin alfa injection: 60 mcg** Each 0.30 ml single dose prefilled syringe contains: Darbepoetin alfa (r-DNA origin) 60 mcg
7	**Darbepoetin alfa injection: 100 mcg** Each 0.50 ml single dose prefilled syringe contains: Darbepoetin alfa (r-DNA origin) 100 mcg
8	**Darbepoetin alfa injection: 150 mcg** Each 0.30 ml single dose prefilled syringe contains: Darbepoetin alfa (r-DNA origin) 150 mcg
9	**Darbepoetin alfa injection: 200 mcg** Each 0.40 ml single dose prefilled syringe contains: Darbepoetin alfa (r-DNA origin) 200 mcg
10	**Darbepoetin alfa injection: 300 mcg** Each 0.60 ml single dose prefilled syringe contains: Darbepoetin alfa (r-DNA origin) 300 mcg
11	**Darbepoetin alfa injection: 500 mcg** Each 1.0 ml single dose prefilled syringe contains: Darbepoetin alfa (r-DNA origin) 500 mcg

Darbepoetin alfa injection of different strengths is filled in prefilled syringes (type 1 glass) of 1 ml capacity, which is with fixed stainless steel needle and needle shield. The syringe is stoppered with a pre-sterilized elastomeric butyl rubber stopper. Then plunger rod is inserted to this syringe.
The approved vial label with batch details is affixed on the glass vial. The labeled glass vial is placed into the carton box along with one package insert.

The Darbepoetin alfa PFS label with batch details is affixed on the 1ml syringe barrel and the approved labeled PFS is fixed with the plunger rod. Then the plunger rod fixed PFS is kept inside the PVC tray. One such pre-filled syringe with tray is placed in blister card and sealed. The sealed blister card with one PI is placed into one carton.

Pack size of 1 pre-filled syringes.

6.6 Special precautions for disposal

Darbepoetin alfa injection is a sterile but unpreserved product. Do not administer more than one dose per syringe. Any medicinal product remaining in the pre-filled syringe should be disposed of.
Before administration the Darbepoetin alfa solution should be inspected for visible particles. Only solutions which are colorless, clear should be injected. Do not shake. Allow the pre-filled syringe to reach room temperature before injecting.

7.0 Marketing Authorisation Holder

Hetero Biopharma Limited,

Sy. No. 458 (Part), TSIIC-
Formulation SEZ, Polepalle Village,
Jadcherla Mandal Mahabubnagar
District – 509 301, Telangana State,
India.

8.0 Marketing Authorization Number

H2019/CTD5182/1062ER

9.0 Date of first authorization / renewal of the authorization

10.0 Date of Revision of the text

March 2026