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

Darbepoetin alfa Injection 25mcg / 40mcg

BIONESP® 25/40 बायोनेस्प २५/४०

DESCRIPTION
Darbepoetin alfa is an erythropoiesis stimulating protein and it has the same mechanism of action as endogenous erythropoietin. Darbepoetin alfa is produced in Chinese Hamster Ovary (CHO) cell line by recombinant DNA technology and is made of 165 amino acids with a molecular weight of about 37 kDa. Compared to Erythropoietin, darbepoetin alfa has two additional N-linked glycosylation sites i.e., 5 N-linked glycosylation sites instead of 3 N-linked glycosylation sites in EPO. The additional N-linked glycosylation sites result in longer half-life (about 3 times higher than EPO) in the human body. Darbepoetin alfa is formulated as a sterile, colorless, preservative-free protein solution for subcutaneous or intravenous injection .

COMPOSITION
Darbepoetin alfa is available in 25 and 40 mcg dose strengths. 25mcg/0.42 mL, 40mcg/0.40mL.
Each dose contains excipients viz., Polysorbate 80, Sodium phosphate monobasic monohydrate, Sodium phosphate dibasic anhydrous and Sodium chloride in Water for injection with pH 6.2±0.2.

Detailed composition of each strength is as under:

S. No	Ingredients	25 mcg /0.42 mL	40 mcg /0.40 mL
1	Darbepoetin alfa (r-DNA origin) (Active ingredient)	25 mcg	40 mcg
2	Monobasic Sodium Phosphate (Monohydrate) IP (as buffering agent)	0.89 mg	0.85 mg
3	Sodium Phosphate Dibasic Anhydrous USP (as buffering agent)	0.28 mg	0.26 mg
4	Sodium Chloride IP (as tonicity agent)	3.44 mg	3.27 mg
5	Polysorbate 80 IP (as stabilizer)	0.021 mg	0.020 mg
6	Water for Injections IP	q.s. to 0.42 mL	q.s. to 0.40 mL

INDICATION
Darbepoetin alfa injection is indicated for the treatment of
- Anemia with Chronic Kidney Disease (CKD) including patients on dialysis and patients not on dialysis
- Treatment of symptomatic anemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy.

DOSAGE AND ADMINISTRATION
Adults and pediatrics:
- **Chronic Kidney Disease Patients:**

Darbepoetin alfa is administered subcutaneously or intravenously as a single weekly injection. When Darbepoetin alfa therapy is initiated or adjusted, the hemoglobin should be followed weekly until stabilized and monitored at least monthly thereafter. During therapy, hematological parameters should be monitored regularly. Doses must be individualized to ensure that hemoglobin is maintained at an appropriate level for each patient. For patients who respond to Darbepoetin alfa with a rapid increase in hemoglobin (e.g., more than 1 g/dL in any 2-week period), the dose of Darbepoetin alfa should be reduced.

Treatment of paediatric patients younger than 1 year of age has not been studied in randomised clinical trials.

Correction of Anemia
For patients ⩾1 year of age, the initial dose by subcutaneous or intravenous administration is 0.45mcg/kg body weight, as a single injection once weekly. Alternatively, in patients not receiving dialysis, an initial dose of 0.75 mcg/kg may be administered subcutaneously as a single injection once every 2 weeks or 1.5 mcg/kg once monthly.

If hemoglobin excursions outside the recommended range occur, the Darbepoetin alfa dose should be adjusted as described below.

Correction of anemia in pediatric patients with Darbepoetin alfa once monthly dosing frequency has not been studied.

Maintenance Dose
The dose should be adjusted for each patient to achieve and maintain hemoglobin levels within the recommended range of 10 to 12 g/dL. If hemoglobin excursions outside the recommended range occur, the Darbepoetin alfa dose should be adjusted. Increase in dose should not be made more frequently than once a month.

For pediatric patients ≥ 1 year of age, in the maintenance phase, Darbepoetin alfa may continue to be administered as a single injection once weekly or once every two weeks. Patients < 6 years of age may need higher doses for maintenance of haemoglobin than patients above that age. 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 ≥ 11 years of age not on dialysis, once the target hemoglobin has been achieved with once every two week dosing, Darbepoetin alfa may be administered subcutaneously once monthly using an initial dose equal to twice the previous.

Dose Adjustment
If the hemoglobin is increasing and approaching 12 g/dL, the dose should be reduced by approximately 25%. If the hemoglobin continues to increase, doses 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%.

If the increase in hemoglobin is less than 1 g/dL over 4 weeks and iron stores are adequate, the dose of Darbepoetin alfa may be increased by approximately 25% of the previous dose. Further increases may be made at 4-week intervals until the specified hemoglobin is obtained.

For patients whose hemoglobin does not attain a level within the range of 10 to 12 g/dL with the use of appropriate Darbepoetin alfa dose titrations over a 12-week period.

When changing the route of administration the same dose must be used and the hemoglobin monitored every one or two weeks so that the appropriate dose adjustments can be made to keep the hemoglobin at the desired level.
- Do not administer higher Darbepoetin alfa doses and use the lowest dose that will maintain a hemoglobin level sufficient to avoid the need for recurrent RBC transfusions,
- Evaluate and treat for other causes of anemia and
- Thereafter, continue to monitor hemoglobin level and if responsiveness improves, Darbepoetin alfa dose adjustments should be made as described above; discontinue Darbepoetin alfa if responsiveness does not improve and the patient needs recurrent RBC transfusions.

Conversion from Epoetin alfa to Darbepoetin alfa
The starting weekly dose of Darbepoetin alfa for adults and pediatric patients is estimated on the basis of the weekly Epoetin alfa dose at the time of substitution. Because of variability, doses should be titrated to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL. Due to the longer serum half-life, Darbepoetin alfa should be administered less frequently than Epoetin alfa. Darbepoetin alfa should be administered once a week if a patient is receiving Epoetin alfa 2 to 3 times weekly. Darbepoetin alfa should be administered once every 2 weeks if a patient is receiving Epoetin alfa once weekly. The subcutaneous or intravenous route of administration should be maintained.

Previous Weekly Epoetin alfa Dose (Units/week)	Weekly Darbepoetin alfa Dose (mcg/week)	
	Adult	Pediatric
< 1,500	6.25	See text*
1,500 to 2,499	6.25	6.25
2,500 to 4,999	12.5	10
5,000 to 10,999	25	20
11,000 to 17,999	40	40
18,000 to 33,999	60	60
34,000 to 89,999	100	100
90,000	200	200

*For pediatric patients receiving a weekly Epoetin alfa dose of < 1,500 Units/week, the available data are insufficient to determine Darbepoetin alfa conversion dose.

Patients on Cancer Chemotherapy
Initiate darbepoetin alfa in patients on cancer chemotherapy only if the hemoglobin is less than 10 g/dL, and if there is a minimum of two additional months of planned chemotherapy.
Use the lowest dose of darbepoetin alfa necessary to avoid RBC transfusions.
Recommended Starting Dose
The recommended starting dose and schedules are:
- 2.25 mcg/kg every week subcutaneously until completion of a chemotherapy course
- 500 mcg every 3 weeks subcutaneously until completion of a chemotherapy course

Dose Adjustment

Dose Adjustment	Weekly Schedule	Every 3 Week Schedule
·If hemoglobin increases greater than 1 g/dL in any 2-week period or ·If hemoglobin reaches a level needed to avoid RBC transfusion	·Reduce dose by 40%	·Reduce dose by 40%
·If hemoglobin exceeds a level needed to avoid RBC transfusion	·Withhold dose until hemoglobin approaches a level where RBC transfusions may be required ·Reinitiate at a dose 40% below the previous dose	·Withhold dose until hemoglobin approaches a level where RBC transfusions may be required ·Reinitiate at a dose 40% below the previous dose
·If hemoglobin increases by less than 1 g/dL and remains below 10 g/dL after 6 weeks of therapy	·Increase dose to 4.5 mcg/kg/week	·No dose adjustment
·If there is no response as measured by hemoglobin levels or if RBC transfusions are still required after 8 weeks of therapy ·Following completion of a chemotherapy course	·Discontinue Darbepoetin alfa	·Discontinue Darbepoetin alfa

Use in Hepatically Impaired Patients
No data is available in patients with impaired liver function. Since the liver is thought to be the principal route of elimination of darbepoetin alfa and rHuEPO, Darbepoetin alfa should be used with caution in patients with liver disease.

Use in Elderly
No dosage adjustment is recommended.

Preparation and administration of Darbepoetin alfa injection
Do not shake Darbepoetin alfa pre-filled syringe. After removing the prefilled syringe from the refrigerator, protect from light until administration. Vigorous shaking or exposure to light may damage Darbepoetin alfa causing it to become biologically inactive. Always store Darbepoetin alfa injection in its carton until use.

Darbepoetin alfa injection should be inspected visually for particulate matter and discoloration prior to administration. Do not use any prefilled syringe showing particulate matter or discoloration.
Do not dilute Darbepoetin alfa injection.

Darbepoetin alfa contains no preservatives. Discard any unused portion of injection immediately. Do not use, if the Darbepoetin alfa injection is expired.

USE IN SPECIAL POPULATION
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.

Lactation
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.

Paediatric Use
Safety and efficacy in the initial treatment of anemic paediatric CKD patients or in the conversion from another erythropoietin to Darbepoetin alfa in paediatric CRF patients less than 1 year of age and also in pediatric cancer patients have not been established.

Geriatric Use
No differences in safety or efficacy were observed between older and younger patients.

CONTRAINDICATIONS
Darbepoetin alfa is contraindicated in patients with:
- Uncontrolled hypertension
- Known hypersensitivity to the active substance or any of the excipients
- Pure red cell aplasia (PRCA) that begins after treatment with Darbepoetin alfa or other erythropoietin protein drugs

WARNINGS & PRECAUTIONS
Increased Mortality, Serious Cardiovascular Events, Thromboembolic Events, and Stroke
In controlled clinical trials of patients with chronic renal failure comparing higher hemoglobin targets (13 - 14 g/dL) to lower targets (9 - 11.3 g/dL), Darbepoetin alfa and other ESAs (Erythropoiesis-stimulating agents) increased the risk of death, myocardial infarction, stroke, congestive heart failure, thrombosis of hemodialysis vascular access, and other thromboembolic events in the higher target groups.

Using Darbepoetin alfa to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit. Use caution in patients with co-existent cardiovascular disease and stroke. Patients with CKD and an insufficient hemoglobin response to ESAs therapy may be at even greater risk for cardiovascular reactions and mortality than other patients. A rate of hemoglobin rise of greater than 1 g/dL over 2 weeks may contribute to these risks.

Darbepoetin alfa and other ESAs increased the risks for death and serious cardiovascular events in controlled clinical trials of patients with cancer. These events included myocardial infarction and stroke. A rate of hemoglobin rise of > 1 g/dL over 2 weeks may contribute to these risks.
ESAs increased the risk of death in patients undergoing coronary artery bypass graft surgery (CABG) and the risk of deep venous thrombosis (DVT) in patients undergoing orthopedic procedures.

Hypertension
Darbepoetin alfa is contraindicated in patients with uncontrolled hypertension. In Darbepoetin alfa clinical studies, approximately 40% of patients with CKD required initiation or intensification of antihypertensive therapy during the early phase of treatment. Hypertensive encephalopathy and seizures have been reported in patients with CKD receiving Darbepoetin alfa.

Appropriately control hypertension prior to initiation of and during treatment with Darbepoetin alfa. Reduce or withhold Darbepoetin alfa if blood pressure becomes difficult to control. Advise patients of the importance of compliance with antihypertensive therapy and dietary restrictions.

Seizures
Risk of seizures has been reported in patients with CKD when treated with Darbepoetin alfa. During the first several months following initiation of therapy, the presence of premonitory neurologic symptoms should be monitored closely. Patients have to be advised to contact their healthcare practitioner for new-onset seizures, premonitory symptoms, or change in seizure frequency.

Pure Red Cell Aplasia
Cases of pure red cell aplasia (PRCA) with or without other cytopenias that arise following the development of neutralizing antibodies to erythropoietin have been reported in patients treated with Darbepoetin alfa. This has been reported predominantly in patients with CRF receiving ESAs by subcutaneous administration. PRCA has also been reported in patients receiving ESAs for anemia related to hepatitis C treatment (an indication for which darbepoetin alfa is not approved).

Any patient who develops a sudden loss of response to Darbepoetin alfa, accompanied by severe anemia and low reticulocyte count, should be evaluated for the presence of neutralizing antibodies to erythropoietin. Permanently discontinue Darbepoetin alfa in patients who develop PRCA following treatment with Darbepoetin alfa or other erythropoietin protein drugs. Do not switch patients to other ESAs .

Lack or Loss of Hemoglobin Response to Darbepoetin alfa
For lack or loss of hemoglobin response to Darbepoetin alfa, initiate a search for causative factors (e.g., iron deficiency, infection, inflammation, bleeding).

If typical causes of lack or loss of hemoglobin response are excluded, evaluate for PRCA. In the absence of PRCA, follow dosing recommendations for management of patients with an insufficient hemoglobin response to Darbepoetin alfa therapy.

Serious Allergic Reactions
Serious allergic reactions, including anaphylactic reactions, angioedema, skin rash and urticaria, associated with Darbepoetin alfa have been reported. If a serious allergic or anaphylactic reaction occurs, Darbepoetin alfa should be immediately and permanently discontinued and appropriate therapy should be administered.

Dialysis Management
Patients may require adjustments in their dialysis prescriptions after initiation of Darbepoetin alfa. Patients receiving darbepoetin alfa may require increased anticoagulation with heparin to prevent clotting of the extracorporeal circuit during hemodialysis.

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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 anemia 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, 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.
- Increased risk of death when administered to target a haemoglobin of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated for use in this patient population.

In view of the above, in some clinical situations blood transfusion should be the preferred treatment for the management of anemia 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 anemia; life-expectancy; the environment in which the patient is being treated; and patient preference.

In patients with solid tumours or lymphoproliferative malignancies, if the haemoglobin value exceeds 12 g/dL, the dosage adaptation described in "Dosage and Administration" 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.

Laboratory Tests
Evaluate transferrin saturation and serum ferritin prior to and during Darbepoetin alfa treatment. Administer supplemental iron therapy when serum ferritin is less than 100mcg/L or when serum transferrin saturation is less than 20%. The majority of patients with CKD will require supplemental iron during the course of ESAs therapy. Following initiation of therapy and after each dose adjustment, monitor hemoglobin weekly until the hemoglobin is stable and sufficient to minimize the need for RBC transfusion. Thereafter, hemoglobin may be monitored less frequently provided hemoglobin levels remain stable.

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

DRUG INTERACTIONS
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.

ADVERSE REACTIONS
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
- 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.

PRECLINICAL 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. In all studies in rats and dogs 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.

OVERDOSE AND MANAGEMENT
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.

PHARMACODYNAMIC & PHARMACOKINETIC PROPERTIES
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.

Pharmacokinetics
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.

Adult Patients with CKD
Following subcutaneous administration of Darbepoetin alfa to patients with CKD (receiving or not receiving dialysis), absorption was slow and C_{max} occurred at 48 hours (range: 12 to 72 hours). In patients with CKD receiving dialysis, the average $t_{½}$ was 46 hours (range: 12 to 89 hours), and in patients with CKD not receiving dialysis, the average $t_{½}$ was 70 hours (range: 35 to 139 hours). Darbepoetin alfa apparent clearance was approximately 1.4 times faster on average in patients receiving dialysis compared to patients not receiving dialysis. The bioavailability of Darbepoetin alfa in patients with CKD receiving dialysis after subcutaneous administration was 37% (range: 30% to 50%).

Following intravenous administration of Darbepoetin alfa to patients with CKD receiving dialysis, Darbepoetin alfa serum concentration-time profiles were biphasic, with a distribution half-life of approximately 1.4 hours and a mean terminal half-life ($t_{½}$) of 21 hours. The $t_{½}$ of Darbepoetin alfa was approximately 3-fold longer than that of epoetin alfa when administered intravenously.

Pediatric Patients with CKD
Following a single subcutaneous Darbepoetin alfa dose in pediatric patients (age 3 to 16 years) with CKD receiving or not receiving dialysis, C_{max} and $t_{½}$ were similar to those obtained in adult patients with CKD on dialysis. Following a single subcutaneous dose, the average bioavailability was 54% (range: 32% to 70%), which was higher than that obtained in adult patients with CKD on dialysis.

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.

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

SHELF LIFE: Please refer to carton/label.
Please see Mfg. Date/Expiry Date printed on pack. Do not use the product after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.

PACKAGING INFORMATION
The following presentations are available:

1 Darbepoetin alfa injection: 25 mcg
Each 0.42 mL single dose pre-filled syringe contains: Darbepoetin alfa (r-DNA origin) 25 mcg

2 Darbepoetin alfa injection: 40 mcg
Each 0.40 mL single dose pre-filled syringe contains: Darbepoetin alfa (r-DNA origin) 40 mcg

Darbepoetin alfa injection of different strengths is filled in pre-filled syringes 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 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.

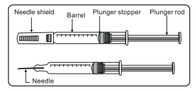
STORAGE & HANDLING INSTRUCTIONS
Store at 2°C to 8°C. Do not freeze or shake. Protect from light.

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 off.

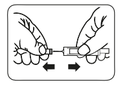
Before administration the Darbepoetin alfa solution should be inspected for visible particles. Only solutions which are colorless, clear should be injected. Do not shake. Allow the pre-filled syringe to reach room temperature before injecting.

Keep out of reach of children.

INSTRUCTIONS FOR USE



Step 1.

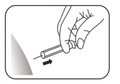


Remove the needle shield by pulling it straight off the syringe.

Step 2.

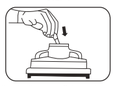
Inject using the usual technique. Push the plunger to the bottom of the syringe body.

STEP 3



Remove the syringe from the injection site keeping your finger on the plunger rod.

STEP 4



Immediately dispose off the syringe using a suitable container.

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Bengaluru - 560 100, India.

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