Full prescribing information

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration: Subcutaneous

Dosage Form / Strength: Darbepoetin alfa is available in 25, 40, 60, 100, 150, 200, 300 and 500 mcg dose strengths. 25 mcg/0.42 ml, 40 mcg/0.40 ml, 60 mcg/0.3 ml, 100 mcg/0.5 ml, 150 mcg/0.3 ml, 200 mcg/0.4 ml, 300 mcg/0.6 ml and 500 mcg/1.0 ml

DESCRIPTION

Darbepoetin alfa is an erythropoiesis stimulating protein and it has the same mechanism of action as 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 injection.

INDICATIONS AND CLINICAL USE

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 anemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy.

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
- with sensitivity to mammalian cell-derived products
- with sensitivity to albumin (where applicable with the albumin formulation)

WARNINGS AND 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 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 ESA 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 chronic renal failure 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.

Effect on tumor growth

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

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

- Shortened time to tumor 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

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 erythropoietin 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 tumor 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 tumors or lymphoproliferative malignancies, if the haemoglobin value exceeds 12 g/dl (7.5 mmol/l), the dosage adaptation described in "**Dosage and Administration**" should be closely respected, in order to minimize 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 ESA 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.

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, rash/erythema, edema and injection site pain.

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.

DOSAGE AND ADMINISTRATION

Chronic Renal Failure Patients / Chronic Kidney Disease Patients

Darbepoetin alfa is administered subcutaneously 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.

Correction of Anemia

The initial dose by subcutaneous administration is 0.45 mcg/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.

The use of Darbepoetin alfa in pediatric chronic renal failure patients as the initial treatment to correct anemia has not been studied.

Maintenance Dose

The dose should be adjusted for each patient to achieve and maintain hemoglobin levels within the 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.

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.

- 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, hemoglobin should continue to be monitored 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 per week. The subcutaneous route of administration should be maintained.

Table 1: Dose Conversions from Epoetin alfa to Darbepoetin alfa

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

Table 2: 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 dosage adjustment is recommended in patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment.

Use in Elderly

No dosage adjustment is recommended.

Preparation and administration of Darbepoetin alfa injection

- Do not shake Darbepoetin alfa injection containing prefilled 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.

OVERDOSAGE

- 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 polycythemia 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 polycythemia, Darbepoetin alfa should be temporarily withheld. If clinically indicated, phlebotomy may be performed.

ACTION AND CLINICAL PHARMACOLOGY

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 erythropoietin (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 $t_{1/2}$ was 46 hours (range: 12 to 89 hours), and in patients with CKD not receiving dialysis, the average $t_{1/2}$ 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 ($t_{1/2}$) of 21 hours. The $t_{1/2}$ 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 $t_{1/2}$ 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 characterization of the terminal half-life. In this study, mean (SD) terminal half-life was 74 (SD 27) hours.

STORAGE AND STABILITY

- 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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Darbepoetin alfa is available in 25, 40, 60, 100, 150, 200, 300 and 500mcg dose strengths. 25mcg/0.42 ml, 40mcg/0.40ml, 60mcg/0.3ml, 100mcg/0.5ml, 150mcg/0.3ml, 200mcg/0.4ml, 300mcg/0.6ml and 500mcg/1.0ml.

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.

Table 3: Detailed composition of each strength is as under

S. No.	Ingredients	25mcg/ 0.42ml	40mcg/ 0.4ml	60mcg/ 0.3ml	100mcg /0.5ml	150mcg /0.3ml	200mcg /0.4ml	300mcg /0.6ml	500mcg /1.0ml
1	Darbepoetin alfa	25mcg	40mcg	60mcg	100mcg	150mcg	200mcg	300mcg	500mcg
2	Sodium phosphate monobasic monohydrate	0.89 mg	0.85 mg	0.64 mg	1.06 mg	0.64 mg	0.85 mg	1.27 mg	2.12 mg
3	Sodium phosphate dibasic anhydrous	0.28 mg	0.26 mg	0.20 mg	0.33 mg	0.20 mg	0.26 mg	0.40 mg	0.66 mg
4	Sodium chloride	3.44 mg	3.27 mg	2.45 mg	4.09 mg	2.45 mg	3.27 mg	3.44 mg	8.18 mg
5	Polysorbate 80	0.021 mg	0.020 mg	0.015 mg	0.025 mg	0.015 mg	0.020 mg	0.03 mg	0.05 mg
6	Water for Injection	q.s. to 0.42 ml	q.s. to 0.4 ml	q.s. to 0.3 ml	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

The following presentations are available:

1 Darbepoetin alfa injection: 25 mcg

Each 0.42 ml single dose prefilled syringe contains: Darbepoetin alfa (r-DNA origin) 25 mcg

2 Darbepoetin alfa injection: 40 mcg

Each 0.40 ml single dose prefilled syringe contains: Darbepoetin alfa (r-DNA origin) 40 mcg

3 Darbepoetin alfa injection: 60 mcg

Each 0.30 ml single dose prefilled syringe contains: Darbepoetin alfa (r-DNA origin) 60 mcg

4 Darbepoetin alfa injection: 100 mcg

Each 0.50 ml single dose prefilled syringe contains: Darbepoetin alfa (r-DNA origin) 100 mcg

5 Darbepoetin alfa injection: 150 mcg

Each 0.30 ml single dose prefilled syringe contains: Darbepoetin alfa (r-DNA origin) 150 mcg

6 Darbepoetin alfa injection: 200 mcg

Each 0.40 ml single dose prefilled syringe contains: Darbepoetin alfa (r-DNA origin) 200 mcg

7 Darbepoetin alfa injection: 300 mcg

Each 0.60 ml single dose prefilled syringe contains: Darbepoetin alfa (r-DNA origin) 300 mcg

8 Darbepoetin alfa injection: 500 mcg

Each 1.00 ml single dose prefilled syringe contains: Darbepoetin alfa (r-DNA origin) 500 mcg

Darbepoetin alfa injection of different strengths is filled in prefilled 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.

PART II: SCIENTIFIC INFORMATION-

PHARMACEUTICAL INFORMATION-

- Drug Substance Proper Name: Darbepoetin alfa
- Chemical Name: Novel Erythropoiesis-Stimulating Agent
- Molecular Mass: 37.1 kd (based on known amino acid and carbohydrate structure)
- **Product Characteristics**

  Brand Name (darbepoetin alfa) is an erythropoiesis-stimulating agent produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. The final processed form is a 165-amino acid protein containing 5 N-linked oligosaccharide chains and 1 O-linked oligosaccharide chain.

CLINICAL TRIALS

Disease Overview-

Chronic kidney disease (CKD) is a pathophysiological process with multiple etiologies, resulting in attrition of nephron number and function leading to end-stage renal failure, incidence of which is observed worldwide, not only within the developed world, but also increasingly within the emerging world. Anemia is also frequent in cancer patients with chemotherapy, and has an important negative effect on health-related quality of life (QoL).

The specialized peritubular cells of the kidney that produce Erythropoietin alfa (EPO) are partially or completely damaged as the renal disease progresses. Thus, anemia of CKD results from reduced capacity of the failing kidney to produce adequate amounts of erythropoietin. The anemia of CKD, if left untreated, is associated with impaired quality of life, several physiologic abnormalities including deterioration in cardiac function, and decreased cognition and mental acuity.

The risk of coronary heart disease (CHD) increases when the anemia is not treated, and studies have indicated that anemia in patients with CKD may predispose to ischemic heart disease, heart failure, and premature death.

Higher hemoglobin (Hb) targets have been widely advocated because of data from observational studies showing that higher Hb is associated with improved survival and quality of life.

Erythropoietin is the principal hormone involved in the regulation and maintenance of a physiological level of circulating erythrocyte mass. And when there is progressive destruction of kidney mass, such as in chronic renal failure or in cases where the cytotoxic chemotherapy is damaging to organs such as the kidneys, anemia is likely to be observed due to decreased production of the hormone.

Erythropoietin has been available in synthetic form as Recombinant Human Erythropoietin (rHuEPO). It is a glycoprotein whose biological activity and physical characteristics are comparable to endogenous human erythropoietin. Although rHuEPO is currently available as a treatment for anemia in chronic renal failure, it is required to be administered two or three times weekly in the majority of patients.

The chronic nature of the disease and its treatment means that injections of rHuEPO can have a major impact on patients and care-givers, and a therapy with less frequent administration would offer a significant clinical benefit.

Darbepoetin alfa (INN and generic name; DPO) is a 165-amino acid recombinant glycosylated protein produced in Chinese Hamster Ovary (CHO) cell line by recombinant DNA technology. It is formulated as a sterile colorless, preservative-free solution for IV and SC administration and is available in dosage strengths of 25μg/dose and 40μg/dose.

DPO differs from rHuEPO in that it contains 5 N-linked oligosaccharide chains and has a molecular weight 37kDa and a carbohydrate composition of 51%. These additional chains are accommodated by substitutions at 5 positions along the 165-amino acid backbone, which do not alter the tertiary structure or its biologic activity. The additional carbohydrates result in longer half-life, increased biologic activity, and decreased receptor affinity.

Before the mid-1980s, there were no effective therapies for the treatment of anemia in patients with CKD. Anemic patients were managed primarily by regular blood transfusions and to a lesser extent with anabolic steroids. By 1990, recombinant human erythropoietin (epoetin) was licensed in the United States and Europe for the treatment of anemia associated with chronic renal failure, including patients on dialysis (end-stage renal disease) and patients not on dialysis.

The introduction of erythropoiesis-stimulating agents (ESAs) into everyday clinical practice has greatly improved the care of patients with chronic kidney disease. The development

of DPO arose out of a hypothesis that increasing the sialic acid content of erythropoietin would generate a molecule that was biologically more active in vivo. DPO is metabolically more stable *in vivo*, with a threefold longer half-life than native or recombinant erythropoietin. The clinical implication of this is that patients may obtain the same benefits of anemia correction but with less frequent injections compared with rHuEPO therapy.

Several clinical studies have demonstrated that DPO is efficacious in treating anemia in patients with CKD not receiving dialysis when administered at an every-other-week (Q2W) dosing interval. This dosing regimen has proved efficacious both in study patients converting from previous once-weekly (QW) erythropoietic therapy with rHuEPO and in those naive to erythropoietic therapy. Extending the DPO dosing interval may have advantages for both patients and their healthcare providers.

Darbepoetin alfa is indicated for the

- Treatment of symptomatic anemia associated with chronic renal failure (CRF) in adults and pediatric patients including patients on dialysis and patients not on dialysis.
- Treatment of symptomatic anemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy.

Clinical Trials

Disease Overview

Chronic kidney disease (CKD) is a pathophysiological process with multiple etiologies, resulting in attrition of nephron number and function leading to end-stage renal failure, incidence of which is observed worldwide, not only within the developed world, but also increasingly within the emerging world. Anemia is also frequent in cancer patients with chemotherapy, and has an important negative effect on health-related quality of life (QoL).

The specialized peritubular cells of the kidney that produce Erythropoietin alfa (EPO) are partially or completely damaged as the renal disease progresses. Thus, anemia of CKD results from reduced capacity of the failing kidney to produce adequate amounts of erythropoietin. The anemia of CKD, if left untreated, is associated with impaired quality

of life, several physiologic abnormalities including deterioration in cardiac function, and decreased cognition and mental acuity.

The risk of coronary heart disease (CHD) increases when the anemia is not treated, and studies have indicated that anemia in patients with CKD may predispose to ischemic heart disease, heart failure, and premature death.

Higher hemoglobin (Hb) targets have been widely advocated because of data from observational studies showing that higher Hb is associated with improved survival and quality of life.

Erythropoietin is the principal hormone involved in the regulation and maintenance of a physiological level of circulating erythrocyte mass. And when there is progressive destruction of kidney mass, such as in chronic renal failure or in cases where the cytotoxic chemotherapy is damaging to organs such as the kidneys, anemia is likely to be observed due to decreased production of the hormone.

Erythropoietin has been available in synthetic form as Recombinant human Erythropoietin (rHuEPO). It is a glycoprotein whose biological activity and physical characteristics are comparable to endogenous human erythropoietin. Although rHuEPO is currently available as a treatment for anemia in chronic renal failure, it is required to be administered two or three times weekly in the majority of patients.

The chronic nature of the disease and its treatment means that injections of rHuEPO can have a major impact on patients and care-givers, and a therapy with less frequent administration would offer a significant clinical benefit.

Darbepoetin alfa (INN and generic name; DPO) is a 165 amino acid recombinant glycosylated protein produced in Chinese Hamster Ovary (CHO) cell line by recombinant DNA technology. It is formulated as a sterile colourless, preservative-free solution for IV and SC administration and is available in dosage strengths of 25μg/dose and 40μg/dose.

DPO differs from rHuEPO in that it contains 5 N-linked oligosaccharide chains and has a molecular weight 37kDa and a carbohydrate composition of 51%. These additional chains are accommodated by substitutions at 5 positions along the 165 amino acid backbone, which do not alter the tertiary structure or its biologic activity. The additional

carbohydrates result in longer half-life, increased biologic activity, and decreased receptor affinity.

Before the mid-1980s, there were no effective therapies for the treatment of anemia in patients with CKD. Anemic patients were managed primarily by regular blood transfusions and to a lesser extent with anabolic steroids. By 1990, recombinant human erythropoietin (epoetin) was licensed in the United States and Europe for the treatment of anemia associated with chronic renal failure, including patients on dialysis (end-stage renal disease) and patients not on dialysis.

The introduction of erythropoiesis-stimulating agents (ESAs) into everyday clinical practice has greatly improved the care of patients with chronic kidney disease. The development of DPO arose out of a hypothesis that increasing the sialic acid content of erythropoietin would generate a molecule that was biologically more active in vivo. DPO is metabolically more stable in vivo, with a threefold longer half-life than native or recombinant erythropoietin. The clinical implication of this is that patients may obtain the same benefits of anemia correction but with less frequent injections compared with rHuEPO therapy.

Several clinical studies have demonstrated that DPO is efficacious in treating anemia in patients with CKD not receiving dialysis when administered at an every-other-week (Q2W) dosing interval. This dosing regimen has proved efficacious both in study patients converting from previous once-weekly (QW) erythropoietic therapy with rHuEPO and in those naive to erythropoietic therapy. Extending the DPO dosing interval may have advantages for both patients and their healthcare providers.

Darbepoetin alfa is indicated for the

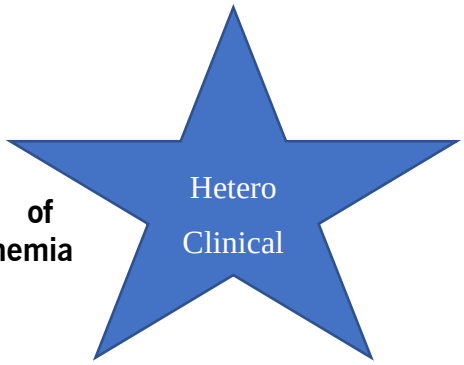
- Treatment of symptomatic anemia associated with chronic renal failure (CRF) in adults and paediatric patients including patients on dialysis and patients not on dialysis.
- Treatment of symptomatic anemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy.

Clinical Trial: Evidences from Clinical Trials- Heading 1

CKD INDUCED ANEMIA- Heading 2

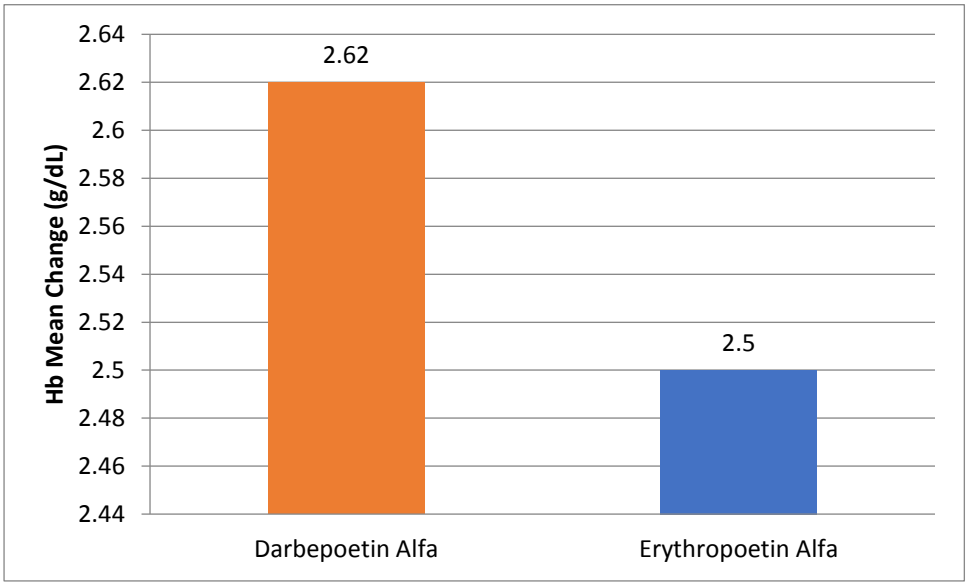
Pre-Dialysis Patients- Heading 3

Randomized, Open Label, Multi-Center phase III Study to Evaluate the Efficacy, Tolerability and Safety of Darbepoetin Alfa as Compared to Erythropoietin in Anemia Associated with Chronic Kidney Disease (CKD)



Primary Efficacy : To study efficacy, tolerability, and safety of Darbepoetin alfa with respect to Erythropoietin alfa for the correction of anemia and maintenance of haemoglobin

associated with Chronic Kidney Disease (CKD) in pre-dialysis patients (N=63), Duration =20 Months



The mean Hb change is found to be 2.62 g/dL vs 2.5 g/dL.

Derise offered early response at 4th week 1.18 g/dL Vs Erythropoietin Alfa 1.16 g/dL.

No of Dose changes required in Derise group was significantly less as compared to Erythropoietin Alfa group.

Conclusion:

In conclusion, this study demonstrates that darbepoetin alfa given at a reduced dose frequency is as effective and well tolerated as erythropoietin alfa for treating renal anemia

in pre-dialysis patients.

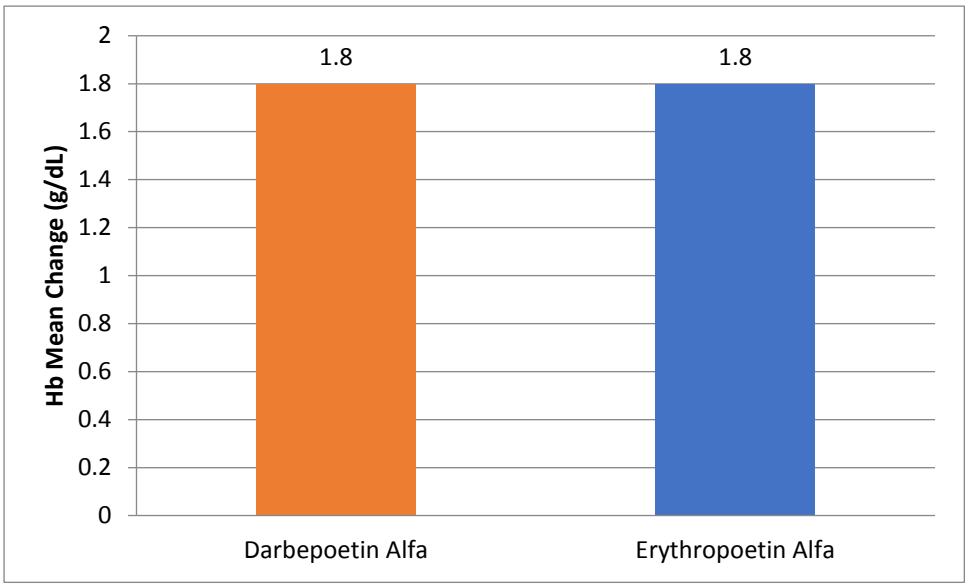
Dialysis Patients

Randomized, Open Label, Multi-Center phase III Study to Evaluate the Efficacy, Tolerability and Safety of Darbepoetin Alfa as Compared to Erythropoietin in Anemia Associated with Chronic Kidney Disease (CKD)

Hetero Clinical

Primary Efficacy:

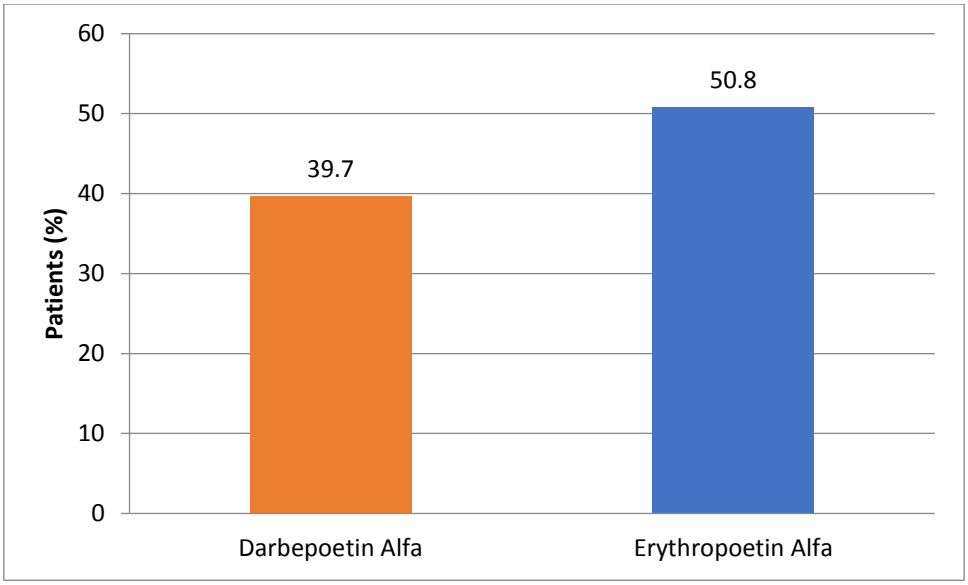
To study efficacy, tolerability, and safety of Darbepoetin alfa with respect to Erythropoietin alfa for the correction of anemia and maintenance of haemoglobin associated with Chronic Kidney Disease (CKD) in dialysis patients. (N=126), Treatment duration = 20 Months



The mean Hb change is found to be at par with Erythropoietin Alfa 1.84. g/dL vs 1.85 g/dL.

Safety

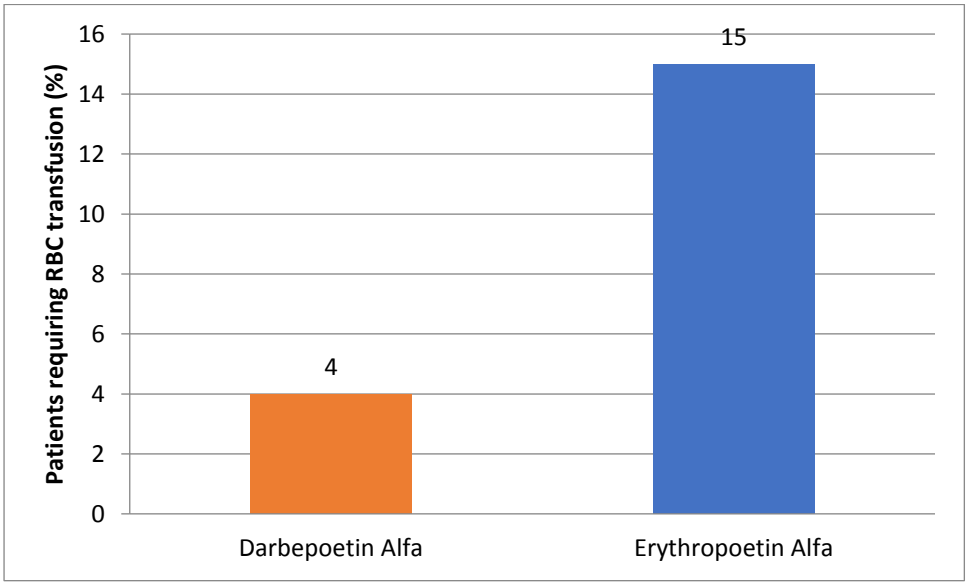
Darbepoetin offers significantly lesser number of patients witnessed at least 1 Treatment Emergent Adverse Events (TEAE) as compared to Erythropoietin (39.7% vs 50.8%



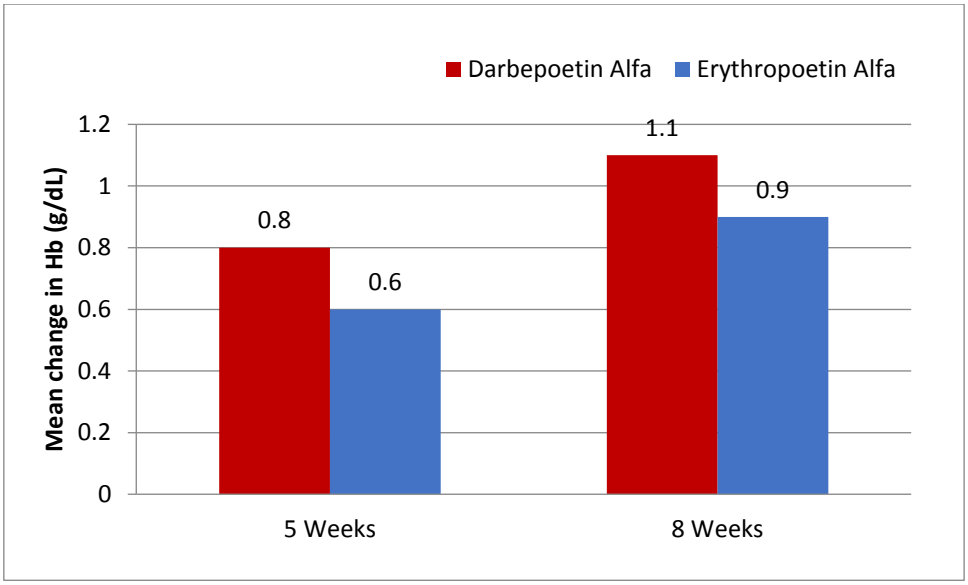
Conclusion

In conclusion, this study demonstrates that darbepoetin alfa given at a reduced dose frequency is as effective and well tolerated as erythropoietin alfa for treating renal anemia in dialysis patients.

Chemotherapy induced anemia- Heading 2



Darbepoetin offered significantly lower incidences of blood transfusions as compared to Erythropoietin group (7% Vs 15%) (QW dosing)



The mean change in Hb levels with Darbepoetin vs Erythropoietin are found to higher with darbepoetin at the end of 5 weeks and 8 weeks of therapy.

Reference

The Oncologist 2004;9:451-458