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

DARBATITOR

1. **Generic Name**

Darbepoetin alfa Injection

2. Qualitative and quantitative composition

DARBATITOR 25

Each pre-filled syringe (0.42 ml) contains:
Darbepoetin alfa (r-DNA origin)……..25 mcg
Monobasic Sodium Phosphate (Monohydrate) I.P. ….0.89 mg
Sodium Phosphate Dibasic Anhydrous U.S.P. ……0.28 mg
Sodium Chloride I.P. ……..……..3.44 mg
Polysorbate 80 I.P. ……...0.021 mg
Water for Injections I.P. …….....q.s. to 0.42 ml

DARBATITOR 40

Each pre-filled syringe (0.40 ml) contains:
Darbepoetin alfa (r-DNA origin)……..40 mcg
Monobasic Sodium Phosphate (Monohydrate) I.P. ….0.85 mg
Sodium Phosphate Dibasic Anhydrous U.S.P. ……0.26 mg
Sodium Chloride I.P. ……..……..3.27 mg
Polysorbate 80 I.P. ……...0.020 mg
Water for Injections I.P. …….....q.s. to 0.40 ml

DARBATITOR 60

Each pre-filled syringe (0.30 ml) contains:
Darbepoetin alfa (r-DNA origin)……..60 mcg
Monobasic Sodium Phosphate (Monohydrate) I.P. ….0.64 mg
Sodium Phosphate Dibasic Anhydrous U.S.P. ……0.20 mg
Sodium Chloride I.P. ……..……..2.45 mg
Polysorbate 80 I.P. ……...0.015 mg
Water for Injections I.P. ……...q.s. to 0.30 ml

3. Dosage form and strength

Dosage form: Pre-filled syringe

Strength: 25mcg/0.42ml, 40mcg/0.40ml and 60mcg/0.30ml

4. Clinical particulars

4.1 Therapeutic indication

It is indicated for the treatment of Anemia with chronic renal failure including patients on dialysis and patients not on dialysis.

4.2 Posology and method of administration

DARBATITOR treatment should be initiated by physicians experienced in the above mentioned indications.

Posology

Treatment of symptomatic anaemia in adult and paediatric 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. DARBATITOR 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 DARBATITOR 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 DARBATITOR doses in patients with chronic renal failure. In patients with a poor haemoglobin response to DARBATITOR, 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 DARBATITOR 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, DARBATITOR 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 DARBATITOR should initially receive a dose equivalent to twice the previous once weekly dose.

In patients not on dialysis, DARBATITOR may continue to be administered as a single injection once weekly or once every two weeks or once monthly. For patients treated with DARBATITOR once every two weeks, after the target haemoglobin has been achieved, DARBATITOR 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 DARBATITOR. The initial weekly dose of DARBATITOR (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 DARBATITOR (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 DARBATITOR for r-HuEPO the haemoglobin should be monitored every one or two weeks and the same route of administration should be used.

Paediatric population with chronic renal failure

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

Correction phase:

For patients ≥ 1 year of age, 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, an initial dose of 0.75 mcg/kg may be administered subcutaneously as a single injection once every two weeks. 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%, 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.

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

Correction of anaemia in paediatric patients with once monthly DARBATITOR dosing frequency has not been studied.

Maintenance phase:

For paediatric patients ≥ 1 year of age, in the maintenance phase, DARBATITOR 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 DARBATITOR 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 haemoglobin has been achieved with once every two week dosing, DARBATITOR may be administered subcutaneously once monthly using an initial dose equal to twice the previous once every two week dose.

Clinical data in paediatric patients has demonstrated that patients receiving r-HuEPO two or three times weekly may be converted to once weekly DARBATITOR, and those receiving r-HuEPO once weekly may be converted to once every other week DARBATITOR. The initial weekly paediatric dose of DARBATITOR (mcg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. The initial every other week dose of DARBATITOR (mcg/every other week) can be determined by dividing the total cumulative dose of r-HuEPO administered over a two-week period by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting DARBATITOR for r-HuEPO the haemoglobin should be monitored every one or two weeks and the same route of administration should be used.

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.

Patients starting dialysis during treatment with DARBATITOR should be closely monitored for adequate control of their haemoglobin.

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.

Treatment of symptomatic chemotherapy-induced anaemia in cancer patients

DARBATITOR 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.

DARBATITOR 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 DARBATITOR 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 DARBATITOR 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%.

Method of administration

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

DARBATITOR 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.

4.3 Contraindications

DARBATITOR is contraindicated in patients with:

- Uncontrolled hypertension.
- Pure red cell aplasia (PRCA) that begins after treatment with DARBATITOR or other erythropoietin protein drugs.
- Serious allergic reactions to DARBATITOR.

4.4 Special warnings and precautions for use

Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism

• In controlled clinical trials of patients with CKD comparing higher hemoglobin targets (13 - 14 g/dL) to lower targets (9 - 11.3 g/dL), DARBATITOR 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 DARBATITOR 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 coexistent 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.

• In controlled clinical trials of patients with cancer, DARBATITOR and other ESAs increased the risks for death and serious adverse cardiovascular reactions. These adverse reactions included myocardial infarction and stroke.

• In controlled clinical trials, 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. The design and overall results of the 3 large trials comparing higher and lower hemoglobin targets are shown in below table.

Randomized Controlled Trials Showing Adverse Cardiovascular Outcomes in Patients with CKD

	Normal Hematocrit Study (NHS) (N = 1265)	**CHOIR (N = 1432)**	**TREAT (N = 4038)**
Time Period of Trial	1993 to 1996	2003 to 2006	2004 to 2009
Population	CKD patients on hemodialysis with coexisting CHF or CAD, hematocrit 30 ± 3% on epoetin alfa	CKD patients not on dialysis with hemoglobin < 11 g/dL not previously administered epoetin alfa	CKD patients not on dialysis with type II diabetes, hemoglobin ≤ 11 g/dL

Hemoglobin Target; Higher vs. Lower (g/dL)	14.0 vs. 10.0	13.5 vs. 11.3	13.0 vs. ≥ 9.0
Median (Q1, Q3) Achieved Hemoglobin level (g/dL)	12.6 (11.6, 13.3) vs. 10.3 (10.0, 10.7)	13.0 (12.2, 13.4) vs. 11.4 (11.1, 11.6)	12.5 (12.0, 12.8) vs. 10.6 (9.9, 11.3)
Primary Endpoint	All-cause mortality or non-fatal MI	All-cause mortality, MI, hospitalization for CHF, or stroke	All-cause mortality, MI, myocardial ischemia, heart failure, and stroke
Hazard Ratio or Relative Risk (95% CI)	1.28 (1.06 - 1.56)	1.34 (1.03 - 1.74)	1.05 (0.94 - 1.17)
Adverse Outcome for Higher Target Group	All-cause mortality	All-cause mortality	Stroke
Hazard Ratio or Relative Risk (95% CI)	1.27 (1.04 - 1.54)	1.48 (0.97 - 2.27)	1.92 (1.38 - 2.68)

Patients with Chronic Kidney Disease

Normal Hematocrit Study (NHS): A prospective, randomized, open-label study of 1265 patients with chronic kidney disease on dialysis with documented evidence of congestive heart failure or ischemic heart disease was designed to test the hypothesis that a higher target hematocrit (Hct) would result in improved outcomes compared with a lower target Hct. In this study, patients were randomized to epoetin alfa treatment targeted to a maintenance hemoglobin of either 14 ± 1 g/dL or 10 ± 1 g/dL. The trial was terminated early with adverse safety findings of higher mortality in the high hematocrit target group. Higher mortality (35% vs. 29%) was observed for the patients randomized to a target hemoglobin of 14 g/dL than for the patients randomized to a target hemoglobin of 10 g/dL. For all-cause mortality, the HR = 1.27; 95% CI (1.04, 1.54); p=0.018. The incidence of nonfatal myocardial infarction, vascular access thrombosis, and other thrombotic events was also higher in the group randomized to a target hemoglobin of 14 g/dL.

CHOIR: A randomized, prospective trial, 1432 patients with anemia due to CKD who were not undergoing dialysis and who had not previously received epoetin alfa therapy were randomized to epoetin alfa treatment targeting a maintenance hemoglobin concentration of either 13.5 g/dL or 11.3 g/dL. The trial was terminated early with adverse safety findings. A major cardiovascular event (death, myocardial infarction, stroke, or hospitalization for congestive heart failure) occurred in 125 of the 715 patients

(18%) in the higher hemoglobin group compared to 97 of the 717 patients (14%) in the lower hemoglobin group [hazard ratio (HR) 1.34, 95% CI: 1.03, 1.74; p = 0.03].

TREAT: A randomized, double-blind, placebo-controlled, prospective trial of 4038 patients with CKD not on dialysis (eGFR of 20 – 60 mL/min), anemia (hemoglobin levels ≤ 11 g/dL), and type 2 diabetes mellitus, patients were randomized to receive either DARBATITOR treatment or a matching placebo. Placebo group patients also received DARBATITOR when their hemoglobin levels were below 9 g/dL. The trial objectives were to demonstrate the benefit of DARBATITOR treatment of the anemia to a target hemoglobin level of 13 g/dL, when compared to a "placebo" group, by reducing the occurrence of either of two primary endpoints: (1) a composite cardiovascular endpoint of all-cause mortality or a specified cardiovascular event (myocardial ischemia, CHF, MI, and CVA) or (2) a composite renal endpoint of all-cause mortality or progression to end stage renal disease. The overall risks for each of the two primary endpoints (the cardiovascular composite and the renal composite) were not reduced with DARBATITOR treatment, but the risk of stroke was increased nearly two-fold in the DARBATITOR-treated group versus the placebo group: annualized stroke rate 2.1% vs. 1.1%, respectively, HR 1.92; 95% CI: 1.38, 2.68; p < 0.001. The relative risk of stroke was particularly high in patients with a prior stroke: annualized stroke rate 5.2% in the DARBATITOR treated group and 1.9% in the placebo group, HR 3.07; 95% CI: 1.44, 6.54. also, among DARBATITOR-treated subjects with a past history of cancer, there were more deaths due to all causes and more deaths adjudicated as due to cancer, in comparison with the control group.

Patients with Cancer

An increased incidence of thromboembolic reactions, some serious and life-threatening, occurred in patients with cancer treated with ESAs.

In a randomized, placebo-controlled study (Study 1 in below table) of 939 women with metastatic breast cancer receiving chemotherapy, patients received either weekly epoetin alfa or placebo for up to a year. This study was designed to show that survival was superior when epoetin alfa was administered to prevent anemia (maintain hemoglobin levels between 12 and 14 g/dL or hematocrit between 36% and 42%). This study was terminated prematurely when interim results demonstrated a higher mortality at 4 months (8.7% vs. 3.4%) and a higher rate of fatal thrombotic reactions (1.1% vs. 0.2%) in the first 4 months of the study among patients treated with epoetin alfa. Based on Kaplan-Meier estimates, at the time of study termination, the 12-month survival was lower in the epoetin alfa group than in the placebo group (70% vs. 76%; HR 1.37, 95% CI: 1.07, 1.75; p = 0.012).

Patients Having Surgery

DARBATITOR is not approved for reduction of RBC transfusions in patients scheduled for surgical procedures.

An increased incidence of DVT in patients receiving epoetin alfa undergoing surgical orthopedic procedures was demonstrated. In a randomized, controlled study, 680 adult patients, not receiving prophylactic anticoagulation and undergoing spinal surgery, received epoetin alfa and standard of care (SOC) treatment (n = 340) or SOC treatment alone (n = 340). A higher incidence of DVTs, determined by either color flow duplex imaging or by clinical symptoms, was observed in the epoetin alfa group (16 [4.7%] patients) compared with the SOC group (7 [2.1%] patients). In addition to the 23 patients with DVTs included in the primary analysis, 19 [2.8%] patients experienced 1

other thrombovascular event (TVE) each (12 [3.5%] in the epoetin alfa group and 7 [2.1%] in the SOC group).

Increased mortality was observed in a randomized, placebo-controlled study of epoetin alfa in adult patients who were undergoing CABG surgery (7 deaths in 126 patients randomized to epoetin alfa versus no deaths among 56 patients receiving placebo). Four of these deaths occurred during the period of study drug administration and all 4 deaths were associated with thrombotic events.

Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence in Patients with Cancer

ESAs resulted in decreased locoregional control/progression-free survival and/or overall survival. These findings were observed in studies of patients with advanced head and neck cancer receiving radiation therapy (Studies 5 and 6), in patients receiving chemotherapy for metastatic breast cancer (Study 1) or lymphoid malignancy (Study 2), and in patients with non-small cell lung cancer or various malignancies who were not receiving chemotherapy or radiotherapy (Studies 7 and 8).

Randomized, Controlled Studies with Decreased Survival and/or Decreased Locoregional Control

Study/Tumor/(n)	**Hemoglobin Target**	**Hemoglobin (Median; Q1, Q3*)**	**Primary Efficacy Outcome**	**Adverse Outcome for ESA-containing Arm**
Chemotherapy				
Study 1 Metastatic breast cancer (n = 939)	12-14 g/dL	12.9 g/dL; 12.2, 13.3 g/dL	12-month overall survival	Decreased 12-month survival
Study 2 Lymphoid malignancy (n = 344)	13-15 g/dL (M) 13-14 g/dL (F)	11 g/dL; 9.8, 12.1 g/dL	Proportion of patients achieving a hemoglobin response	Decreased overall survival
Study 3 Early breast cancer (n = 733)	12.5-13 g/dL	13.1 g/dL; 12.5, 13.7 g/dL	Relapse-free and overall survival	Decreased 3-year relapse-free and overall survival
Study 4 Cervical cancer (n = 114)	12-14 g/dL	12.7 g/dL; 12.1, 13.3 g/dL	Progression-free and overall survival and locoregional control	Decreased 3-year progression-free and overall survival and

				locoregional control
Radiotherapy Alone				
Study 5 Head and neck cancer (n = 351)	≥ 15 g/dL (M) ≥ 14 g/dL (F)	Not available	Locoregional progression-free survival	Decreased 5-year locoregional progression-free and overall survival
Study 6 Head and neck cancer (n = 522)	14-15.5 g/dL	Not available	Locoregional disease control	Decreased locoregional disease control
No Chemotherapy or Radiotherapy				
Study 7 Non-small cell lung cancer (n = 70)	12-14 g/dL	Not available	Quality of life	Decreased overall survival
Study 8 Non-myeloid malignancy (n = 989)	12-13 g/dL	10.6 g/dL; 9.4, 11.8 g/dL	RBC transfusions	Decreased overall survival

* Q1= 25th percentile

Q3= 75th percentile

Decreased Overall Survival

Study 1 was described in the previous section. Mortality at 4 months (8.7% vs. 3.4%) was significantly higher in the epoetin alfa arm. The most common investigator-attributed cause of death within the first 4 months was disease progression; 28 of 41 deaths in the epoetin alfa arm and 13 of 16 deaths in the placebo arm were attributed to disease progression. Investigator-assessed time to tumor progression was not different between the 2 groups. Survival at 12 months was significantly lower in the epoetin alfa arm (70% vs. 76%; HR 1.37, 95% CI: 1.07, 1.75; p = 0.012).

Study 2 was a randomized, double-blind study (darbepoetin alfa vs. placebo) conducted in 344 anemic patients with lymphoid malignancy receiving chemotherapy. With a median follow-up of 29 months, overall mortality rates were significantly higher among patients randomized to darbepoetin alfa as compared to placebo (HR 1.36, 95% CI: 1.02, 1.82).

Study 7 was a multicenter, randomized, double-blind study (epoetin alfa vs. placebo) in which patients with advanced non-small cell lung cancer receiving only palliative radiotherapy or no active therapy were treated with epoetin alfa to achieve and maintain hemoglobin levels between 12 and 14 g/dL. Following an interim analysis of 70 patients (planned accrual 300 patients), a significant difference in survival in favor of the

patients in the placebo arm of the study was observed (median survival 63 vs. 129 days; HR 1.84; p = 0.04).

Study 8 was a randomized, double-blind study (darbepoetin alfa vs. placebo) in 989 anemic patients with active malignant disease, neither receiving nor planning to receive chemotherapy or radiation therapy. There was no evidence of a statistically significant reduction in proportion of patients receiving RBC transfusions. The median survival was shorter in the darbepoetin alfa treatment group than in the placebo group (8 months vs. 10.8 months; HR 1.30, 95% CI: 1.07, 1.57).

Decreased Progression-free Survival and Overall Survival

Study 3 was a randomized, open-label, controlled, factorial design study in which darbepoetin alfa was administered to prevent anemia in 733 women receiving neo-adjuvant breast cancer treatment. A final analysis was performed after a median follow-up of approximately 3 years. The 3-year survival rate was lower (86% vs. 90%; HR 1.42, 95% CI: 0.93, 2.18) and the 3-year relapse-free survival rate was lower (72% vs. 78%; HR 1.33, 95% CI: 0.99, 1.79) in the darbepoetin alfa-treated arm compared to the control arm.

Study 4 was a randomized, open-label, controlled study that enrolled 114 of a planned 460 cervical cancer patients receiving chemotherapy and radiotherapy. Patients were randomized to receive epoetin alfa to maintain hemoglobin between 12 and 14 g/dL or to RBC transfusion support as needed. The study was terminated prematurely due to an increase in thromboembolic adverse reactions in epoetin alfa-treated patients compared to control (19% vs. 9%). Both local recurrence (21% vs. 20%) and distant recurrence (12% vs. 7%) were more frequent in epoetin alfa-treated patients compared to control. Progression-free survival at 3 years was lower in the epoetin alfa-treated group compared to control (59% vs. 62%; HR 1.06, 95% CI: 0.58, 1.91). Overall survival at 3 years was lower in the epoetin alfa-treated group compared to control (61% vs. 71%; HR 1.28, 95% CI: 0.68, 2.42).

Study 5 was a randomized, placebo-controlled study in 351 head and neck cancer patients where epoetin beta or placebo was administered to achieve target hemoglobins $\geq$ 14 and $\geq$ 15 g/dL for women and men, respectively. Locoregional progression-free survival was significantly shorter in patients receiving epoetin beta (HR 1.62, 95% CI: 1.22, 2.14; p = 0.0008) with medians of 406 days and 745 days in the epoetin beta and placebo arms respectively. Overall survival was significantly shorter in patients receiving epoetin beta (HR 1.39, 95% CI: 1.05, 1.84; p = 0.02).

Decreased Locoregional Control

Study 6 was a randomized, open-label, controlled study conducted in 522 patients with primary squamous cell carcinoma of the head and neck receiving radiation therapy alone (no chemotherapy) who were randomized to receive darbepoetin alfa to maintain hemoglobin levels of 14 to15.5 g/dL or no darbepoetin alfa. An interim analysis performed on 484 patients demonstrated that locoregional control at 5 years was significantly shorter in patients receiving darbepoetin alfa (RR 1.44, 95% CI: 1.06, 1.96; p = 0.02). Overall survival was shorter in patients receiving darbepoetin alfa (RR 1.28, 95% CI: 0.98, 1.68; p = 0.08).

Hypertension

DARBATITOR is contraindicated in patients with uncontrolled hypertension. In DARBATITOR 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 DARBATITOR.

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

Seizures

DARBATITOR increases the risk of seizures in patients with CKD. During the first several months following initiation of DARBATITOR, monitor patients closely for premonitory neurologic symptoms. Advise patients to contact their healthcare practitioner for new-onset seizures, premonitory symptoms, or change in seizure frequency.

Lack or Loss of Hemoglobin Response to DARBATITOR

For lack or loss of hemoglobin response to DARBATITOR, 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 DARBATITOR therapy.

Pure Red Cell Aplasia

Cases of PRCA and of severe anemia, with or without other cytopenias that arise following the development of neutralizing antibodies to erythropoietin have been reported in patients treated with DARBATITOR. This has been reported predominantly in patients with CKD 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 DARBATITOR is not approved).

If severe anemia and low reticulocyte count develop during treatment with DARBATITOR, withhold DARBATITOR and evaluate patients for neutralizing antibodies to erythropoietin.

Serious Allergic Reactions

Serious allergic reactions, including anaphylactic reactions, angioedema, bronchospasm, skin rash, and urticaria may occur with DARBATITOR. Immediately and permanently discontinue DARBATITOR and administer appropriate therapy if a serious allergic or anaphylactic reaction occurs.

Dialysis Management

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

Laboratory Monitoring

Evaluate transferrin saturation and serum ferritin prior to and during DARBATITOR treatment. Administer supplemental iron therapy when serum ferritin is less than 100 mcg/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.

4.5 Drugs interactions

No formal drug interaction studies have been conducted with DARBATITOR.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of DARBATITOR use in pregnant women. In animal reproduction and developmental toxicity studies, DARBATITOR increased early post-implantation loss. Use DARBATITOR during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When DARBATITOR was administered intravenously to healthy pregnant rats and rabbits, there was no evidence of embryofetal toxicity or other adverse outcomes at the intravenous doses tested, up to 20 mcg/kg/day. This animal dose level of 20 mcg/kg/day is approximately 20-fold higher than the clinical recommended starting dose, depending on the patient's treatment indication. Slightly reduced fetal weights were observed when healthy rat and rabbit mothers received doses of 1 mcg/kg or more. This dose of 1 mcg/kg is near the clinical recommended starting dose. While no adverse effects on uterine implantation occurred in animals, there was an increase in early post-implantation loss in animal fertility studies. It is not clear whether the increased post-implantation loss reflects a drug effect on the uterine environment or on the conceptus. No significant placental transfer of DARBATITOR was detected.

In a peri/postnatal development study, pregnant female rats received DARBATITOR intravenously every other day from implantation throughout pregnancy and lactation. The lowest dose tested, 0.5 mcg/kg, did not cause fetal toxicity; this dose is approximately equivalent to the clinical recommended starting dose. At maternal doses of 2.5 mcg/kg and higher, pups had decreased fetal body weights, which correlated with a slight increase in the incidence of fetal deaths, as well as delayed eye opening and delayed preputial separation.

Nursing Mothers

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

Pediatric Use

Pediatric Patients with CKD

DARBATITOR safety and efficacy were similar between adults and pediatric patients with CKD who were over 1 year of age when patients were transitioned from treatment with epoetin alfa to DARBATITOR. DARBATITOR safety and efficacy have not been established in the initial treatment of anemic pediatric patients with CKD or in the transition from another erythropoietin to DARBATITOR in pediatric CKD patients less than 1 year of age.

Pediatric Cancer Patients

The safety and efficacy of DARBATITOR in pediatric cancer patients have not been established.

Geriatric Use

Of the 1801 patients with CKD in clinical studies of DARBATITOR, 44% were age 65 and over, while 17% were age 75 and over. Of the 873 patients in clinical studies receiving DARBATITOR and concomitant cancer chemotherapy, 45% were age 65 and over, while 14% were age 75 and over. No differences in safety or efficacy were observed between older and younger patients.

4.7 Effects on ability to drive and use machines

DARBATITOR has no or negligible influence on the ability to drive and use machines

4.8 Undesirable effects

Incidence of adverse reactions from controlled clinical studies and post-marketing experience are:

MedDRA system organ class	**Subject incidence**	**Adverse reaction**
Blood and lymphatic system disorders	Not known[2]	Pure red cell aplasia
Immune system disorders	Very common	Hypersensitivity[a]
Nervous system disorders	Common	Stroke[b]
	Uncommon[1]	Convulsions
Cardiac disorders	Very common	Hypertension
Vascular disorders	Uncommon	Thromboembolic events[c]
	Uncommon[1]	Dialysis vascular access thrombosis[d]
Skin and subcutaneous tissue disorders	Common	Rash/erythema[e]
	Not known[2]	SJS/TEN, erythema multiforme, blistering, skin exfoliation
General disorders and administration site conditions	Common	Injection site pain
	Uncommon[1]	Injection site bruising Injection site haemorrhage

[1] Adverse reactions identified in the post-marketing environment. Per the Guideline on Summary of Product Characteristics (Revision 2, September 2009), frequency of adverse reactions identified in the post-marketing setting was determined using the "Rule of three".

[2] Frequency cannot be estimated from the available data.

[a] Hypersensitivity events includes all events under the hypersensitivity SMQ.

[b] Stroke events includes PT haemorrhagic stroke, ischaemic stroke, cerebrovascular accident, and stroke in evolution.

[c] Thromboembolic events adverse reaction includes PT embolism arterial, thrombophlebitis, thrombosis, venous thrombosis limb.

[d] Dialysis vascular access thrombosis includes all adverse reactions under the dialysis vascular access thrombosis AMQ

[e] Rash/erythema adverse reaction includes PT rash, rash pruritic, rash macular, rash generalised, erythema.

Cancer patients

Adverse reactions were determined based on pooled data from eight randomised, double-blind, placebo-controlled studies with a total of 4,630 patients. Patients with solid tumours (e.g., lung, breast, colon, ovarian cancers) and lymphoid malignancies (e.g., lymphoma, multiple myeloma) were enrolled in the clinical studies.

Incidence of adverse reactions from controlled clinical studies and post-marketing experience are:

MedDRA system organ class	**Subject incidence**	**Adverse reaction**
Immune system disorders	Very common	Hypersensitivity[a]
Nervous system disorders	Uncommon[1]	Convulsions
Cardiac disorders	Common	Hypertension
Vascular disorders	Common	Thromboembolic events[b], including pulmonary embolism
Skin and subcutaneous tissue disorders	Common	Rash/erythema[c]
	Not known[2]	SJS/TEN, erythema multiforme, blistering, skin exfoliation
General disorders and administration site conditions	Common	Oedema[d]
	Common	Injection site pain[e]
	Uncommon[1]	Injection site bruising Injection site haemorrhage

[1] ADRs identified in the post marketing environment. Per the Guideline on Summary of Product Characteristics (Revision 2, September 2009), frequency of ADRs identified in the post marketing setting was determined using the "Rule of three".

[2] Frequency cannot be estimated from the available data.

[a] Hypersensitivity events includes all events under the hypersensitivity SMQ.

[b] Thromboembolic events adverse reactions includes PT embolism, thrombosis, deep vein thrombosis, jugular vein thrombosis, venous thrombosis, arterial thrombosis, pelvic venous thrombosis, peripheral embolism, pulmonary embolism, as well as thrombosis in device from SOC product issues.

[c] Rash adverse reactions includes PT rash, rash pruritic, rash generalised, rash papular, erythema, exfoliative rash, rash maculo-papular, rash vesicular as well as rash pustular from SOC Infections and Infestations.

[d] Oedema: includes PT Oedema Peripheral, Oedema, Generalised Oedema, Oedema due to Cardiac Disease, Face oedema

[e] Injection site pain adverse reaction includes PT injection site pain, administration site pain, catheter site pain, infusion site pain and vessel puncture site pain.

Description of selected adverse reactions

Chronic renal failure patients

Stroke was reported as common in CRF patients in TREAT.

In isolated cases, neutralising anti-erythropoietin antibody mediated pure red cell aplasia (PRCA) associated with darbepoetin therapy have been reported predominantly in patients with CRF treated subcutaneously. In case PRCA is diagnosed, therapy with darbepoetin must be discontinued and patients should not be switched to another recombinant erythropoietic protein.

The frequency of all hypersensitivity reactions was estimated from clinical trial data as very common in CRF patients. Hypersensitivity reactions were also very common in the placebo groups. There have been reports, from post-marketing experience, of serious hypersensitivity reactions including anaphylactic reaction, angioedema, allergic bronchospasm, skin rash and urticaria associated with darbepoetin alfa.

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.

Convulsions have been reported in patients receiving darbepoetin alfa. The frequency is estimated from clinical trial data as uncommon in CRF patients.

In CRF patients on haemodialysis, events of vascular access thrombosis (such as vascular access complication, arteriovenous fistula thrombosis, graft thrombosis, shunt thrombosis, arteriovenous fistula site complication, etc.) have been reported in post-marketing data. The frequency is estimated from clinical trial data as uncommon.

Cancer patients

Hypertension has been observed in cancer patients in post-marketing experience. The frequency is estimated from clinical trial data as common in cancer patients and was also common in the placebo groups.

Hypersensitivity reactions have been observed in cancer patients in post-marketing experience. The frequency of all hypersensitivity reactions was estimated from clinical trial data as very common in cancer patients. Hypersensitivity reactions were also very common in the placebo groups. There have been reports of serious hypersensitivity reactions including anaphylactic reaction, angioedema, allergic bronchospasm, skin rash and urticaria associated with darbepoetin alfa.

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.

Convulsions have been reported in patients receiving darbepoetin alfa in post-marketing experience. The frequency is estimated from clinical trial data as uncommon in cancer patients. Convulsions were common in the placebo groups.

Paediatric chronic renal failure population

In all paediatric CRF studies, there were no additional adverse reactions identified for paediatric patients compared to those previously reported for adult patients.

4.9 Overdose

DARBATITOR overdosage can cause hemoglobin levels above the desired level, which should be managed with discontinuation or reduction of DARBATITOR dosage and/or with phlebotomy, as clinically indicated. Cases of severe hypertension have been observed following overdose with ESAs.

5. Pharmacological properties

Pharmacotherapeutic group:

ATC code: B03XA02

5.1 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 anaemia is due to erythropoietin deficiency. In patients with cancer receiving chemotherapy the etiology of anaemia is multifactorial. In these patients, erythropoietin deficiency and a reduced response of erythroid progenitor cells to endogenous erythropoietin both contribute significantly towards their anaemia.

5.2 Pharmacodynamic properties

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.

5.3 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.

<u>Chronic renal failure patients</u>

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 darbepoetin 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 mcg/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 mcg/kg weekly and 3 to 9 mcg/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 anaemia treated with 6.75 mcg/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.

6. Nonclinical properties

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

The carcinogenic potential of DARBATITOR has not been evaluated in long-term animal studies. In toxicity studies of approximately 6 months duration in rats and dogs, no tumorigenic or unexpected mitogenic responses were observed in any tissue type.

Mutagenicity

DARBATITOR was not mutagenic or clastogenic under the conditions tested. DARBATITOR 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.

Impairment of Fertility

DARBATITOR increased the incidence of post-implantation losses in rats. Male and female rats received intravenous doses prior to and during mating; then females were treated 3 times weekly during the first trimester of gestation (gestation days 1, 3, 5, and

7). No effect on reproductive performance, fertility, or sperm assessment parameters were detected at any of the doses evaluated (up to 10 mcg/kg, administered 3 times weekly). The dose of 10 mcg/kg is more than 10-fold higher than the clinical recommended starting dose. An increase in post-implantation fetal loss was seen at doses equal to or greater than 0.5 mcg/kg, administered 3 times weekly. The dose of 0.5 mcg/kg is approximately equivalent to the clinical recommended starting dose. Signs of exaggerated pharmacology were not observed in the mother receiving 0.5 mcg/kg or less, but were observed at 2.5 mcg/kg and higher.

Reproductive and Developmental Toxicology

When DARBATITOR was administered intravenously during organogenesis to pregnant rats (gestational days 6 to 15) and rabbits (gestational days 6 to 18), no evidence of direct embryotoxic, fetotoxic, or teratogenic outcomes were observed at the doses tested, up to 20 mcg/kg/day. This animal dose level of 20 mcg/kg/day is approximately 20-fold higher than the clinical recommended starting dose, depending on the patient's treatment indication. The only adverse effect observed was a slight reduction in fetal weight, which occurred only at doses causing exaggerated pharmacological effects in both the rat and rabbit dams (1 mcg/kg/day and higher). No deleterious effects on uterine implantation were seen in either species.

No significant placental transfer of DARBATITOR was observed in rats; placental transfer was not evaluated in rabbits.

In a peri/postnatal development study, pregnant female rats were treated intravenously with DARBATITOR day 6 of gestation through day 23 of lactation at 2.5 mcg/kg and higher every other day. Pups of treated mothers had decreased fetal body weights, which correlated with slight increases in the incidences of fetal death, as well as delayed eye opening and delayed preputial separation. The offspring (F1 generation) of the treated rats were observed postnatally; rats from the F1 generation reached maturity and were mated; no DARBATITOR-related effects were apparent for their offspring (F2 generation fetuses).

7. Description

Darbepoetin alfa belongs to Haematopoietic growth factors with Protein Chemical Formula of $C_{815}H_{1317}N_{233}O_{241}S_5$ and Protein Average Weight of 18396.1 Da.

DARBATITOR 25/40/60

Darbepoetin alfa infection is a clear and colorless liquid free from particles that can be observed by visual inspection. The excipients used are Monobasic Sodium Phosphate (Monohydrate), Sodium Phosphate Dibasic Anhydrous, Sodium Chloride, Polysorbate 80 and Water for Injection.

8. Pharmaceutical particulars

8.1 Incompatibilities

None stated

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

DARBATITOR 25

Single dose pre-filled syringe of 0.42ml

DARBATITOR 40

Single dose pre-filled syringe of 0.40ml

DARBATITOR 60

Single dose pre-filled syringe of 0.30ml

8.4 Storage and handing instructions

Store at 2°C to 8°C. Protect from light.

Do not dilute Darbapoetin alfa injection.

Do not use if presence of any particulate matter or discolouration.

Discard any unused portion. Protect from light until administration.

9. Patient counselling information

DARBATITOR

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1 What DARBATITOR is and what it is used for

Your doctor has given you DARBATITOR (an anti-anaemic) to treat your anaemia. Anaemia is when your blood does not contain enough red blood cells and the symptoms may be fatigue, weakness and shortness of breath.

DARBATITOR works in exactly the same way as the natural hormone erythropoietin. Erythropoietin is produced in your kidneys and encourages your bone marrow to produce more red blood cells. The active substance of DARBATITOR is darbepoetin alfa produced by gene-technology in Chinese Hamster Ovary Cells (CHO-K1).

If you have chronic renal failure

DARBATITOR is used to treat symptomatic anaemia that is associated with chronic renal failure (kidney failure) in adults and children. In kidney failure, the kidney does not produce enough of the natural hormone erythropoietin which can often cause anaemia.

Because it will take your body some time to make more red blood cells, it will be about four weeks before you notice any effect. Your normal dialysis routine will not affect the ability of DARBATITOR to treat your anaemia.

If you are receiving chemotherapy

DARBATITOR is used to treat symptomatic anaemia in adult cancer patients with non-bone marrow cancers (non-myeloid malignancies) who are receiving chemotherapy.

One of the main side effects of chemotherapy is that it stops the bone marrow producing enough blood cells. Towards the end of your chemotherapy course, particularly if you have had a lot of chemotherapy, your red blood cell count may fall making you anaemic.

9.2 What you need to know before you take DARBATITOR

Do not use DARBATITOR:

if you are allergic to darbepoetin alfa or any of the other ingredients of this medicine.

if you have been diagnosed with high blood pressure which is not being controlled with other medicines prescribed by your doctor.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using DARBATITOR

Please tell your doctor if you are suffering or have suffered from:

- high blood pressure which is being controlled with medicines prescribed by your doctor;
- sickle cell anaemia;
- epileptic fits (seizures);
- convulsions (fits or seizures);
- liver disease;
- significant lack of response to medicines used to treat anaemia;
- an allergy to latex (the needle cap on the pre-filled pen contains a derivative of latex); or
- hepatitis C

Special warnings:

If you have symptoms which include unusual tiredness and a lack of energy this could mean you have pure red cell aplasia (PRCA), which has been reported in patients. PRCA means that the body has stopped or reduced the production of red blood cells which causes severe anaemia. If you experience these symptoms you should contact your doctor who will determine the best course of action to treat your anaemia.

Take special care with other products that stimulate red blood cell production: DARBATITOR is one of a group of products that stimulate the production of red blood cells like the human protein erythropoietin does. Your healthcare professional should always record the exact product you are using.

If you are a patient with chronic renal failure, and particularly if you do not respond properly to DARBATITOR, your doctor will check your dose of DARBATITOR because repeatedly increasing your dose of DARBATITOR if you are not responding

to treatment may increase the risk of having a problem of the heart or the blood vessels and could increase risk of myocardial infarction, stroke and death.

Your doctor should try to keep your haemoglobin between 10 and 12 g/dL. Your doctor will check that your haemoglobin does not exceed a certain level, as high haemoglobin concentrations could put you at risk of having a problem of the heart or the blood vessels and could increase risk of myocardial infarction, stroke and death.

If you have symptoms which include severe headache, drowsiness, confusion, problems with your eyesight, nausea, vomiting or fits (seizures), it could mean that you have very high blood pressure. If you experience these symptoms you should contact your doctor.

If you are a cancer patient you should be aware that DARBATITOR may act as a blood cell growth factor and in some circumstances may have a negative impact on your cancer. Depending on your individual situation a blood transfusion may be preferable. Please discuss this with your doctor.

Misuse by healthy people can cause life-threatening problems with the heart or blood vessels.

Serious skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in association with epoetin treatment. SJS/TEN can appear initially as reddish target-like spots or circular patches often with central blisters on the trunk. Also, ulcers of mouth, throat, nose, genitals and eyes (red and swollen eyes) can occur. These serious skin rashes are often preceded by fever and/or flu-like symptoms. The rashes may progress to widespread peeling of the skin and life-threatening complications.

If you develop a serious rash or another of these skin symptoms, stop taking DARBATITOR and contact your doctor or seek medical attention immediately.

Other medicines and DARBATITOR

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Cyclosporin and tacrolimus (medicines which suppress the immune system) may be affected by the number of red cells in your blood. It is important to tell your doctor if you are taking either of these medicines.

Using DARBATITOR with food and drink

Food and drink do not affect DARBATITOR.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

DARBATITOR has not been tested in pregnant women. It is important to tell your doctor if you:

are pregnant;

think you may be pregnant; or

plan to get pregnant.

It is not known whether darbepoetin alfa is excreted in human milk. You must stop breast-feeding if you use DARBATITOR.

Driving and using machines

DARBATITOR should not affect your ability to drive or use machinery.

9.3 How to take DARBATITOR

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Following blood tests, your doctor has decided you need DARBATITOR as your haemoglobin level is 10 g/dL or less. Your injection is to be given under the skin (subcutaneous), and so you may use the DARBATITOR pre-filled pen. Your doctor will tell you how much and how often you must take DARBATITOR in order to maintain a haemoglobin level between 10 and 12 g/dL. This may vary depending on whether you are an adult or a child.

Injecting DARBATITOR yourself

Your doctor has decided that the DARBATITOR pre-filled pen is the best way for you, a nurse or a carer to inject DARBATITOR. Your doctor, nurse or pharmacist will show you how to inject yourself with the pre-filled pen. Do not try to inject yourself if you have not been trained. Never inject DARBATITOR into a vein yourself. The pre-filled pen is designed to inject the area under your skin only.

If you have chronic renal failure

For all adult and paediatric patients ≥ 1 year of age with chronic renal failure, DARBATITOR pre-filled pen is given as a single injection, under your skin (subcutaneous).

In order to correct your anaemia, your initial dose of DARBATITOR per kilogram of your body weight will be either:

0.75 micrograms once every two weeks, or

0.45 micrograms once weekly.

For adult patients not on dialysis, 1.5 micrograms/kg once monthly may also be used as the initial dose.

For all adult and paediatric patients ≥ 1 year of age with chronic renal failure, once your anaemia is corrected you will continue to receive DARBATITOR given as a single injection, either once a week or once every two weeks. For all adults and paediatric patients ≥ 11 years of age not on dialysis, DARBATITOR could also be given as an injection once monthly.

Your doctor will take regular blood samples to measure how your anaemia is responding and may adjust your dose once every four weeks as necessary in order to maintain long term control of your anaemia.

Your doctor will use the lowest effective dose to control the symptoms of your anaemia.

If you do not respond adequately to DARBATITOR, your doctor will check your dose and will inform you if you need to change doses of DARBATITOR.

Your blood pressure will also be checked regularly, particularly at the beginning of your treatment.

In some cases, your doctor may recommend that you take iron supplements.

Your doctor may decide to change the way that your injection is given (either under the skin or into a vein). If this changes you will start on the same dose as you have been receiving and your doctor will take blood samples to make sure that your anaemia is still being managed correctly.

If your doctor has decided to change your treatment from r-HuEPO (erythropoietin produced by gene-technology) to DARBATITOR, they will choose whether you should receive your DARBATITOR injection once weekly or once every two weeks. The route of injection is the same as with r-HuEPO but your doctor will tell you how much you should take, and when, and may adjust your dose if necessary.

If you are receiving chemotherapy

DARBATITOR is given as a single injection, either once a week or once every three weeks, under your skin.

In order to correct your anaemia, your initial dose will be

500 micrograms once every three weeks (6.75 micrograms of DARBATITOR per kilogram of your body weight), or

2.25 micrograms (once weekly) of DARBATITOR per kilogram of your body weight.

Your doctor will take regular blood samples to measure how your anaemia is responding and may adjust your dose as necessary. Your treatment will continue until approximately four weeks after the end of your chemotherapy. Your doctor will tell you exactly when to stop taking DARBATITOR.

In some cases, your doctor may recommend that you take iron supplements.

If you use more DARBATITOR than you should

You could have serious problems if you use more DARBATITOR than you need, such as very high blood pressure. You should contact your doctor, nurse or pharmacist if this does happen. If you feel unwell in any way you should contact your doctor, nurse or pharmacist immediately.

If you forget to use DARBATITOR

Do not use a double dose to make up for a forgotten dose.

If you have forgotten a dose of DARBATITOR, you should contact your doctor to discuss when you should inject the next dose.

If you stop using DARBATITOR

If you want to stop using DARBATITOR, you should discuss it with your doctor first.

9.4 Possible side effects

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

The following side effects have been experienced by some patients taking DARBATITOR:

Chronic renal failure patients

Very common: may affect more than 1 in 10 people

High blood pressure (hypertension)

Allergic reactions

Common: may affect up to 1 in 10 people

Stroke

Pain around the area injected

Rash and/or redness of the skin

Uncommon: may affect up to 1 in 100 people

Blood clots (thrombosis)

Convulsions (fits and seizures)

Bruising and bleeding at the site of injection

Blood clots in a dialysis access

Not known: frequency cannot be estimated from available data

Pure red cell aplasia (PRCA) – (anaemia, unusual tiredness, lack of energy)

Cancer patients

Very common: may affect more than 1 in 10 people

Allergic reactions

Common: may affect up to 1 in 10 people

High blood pressure (hypertension)

Blood clots (thrombosis)

Pain around the area injected

Rash and/or redness of the skin

Fluid retention (oedema)

Uncommon: may affect up to 1 in 100 people

Convulsions (fits and seizures)

Bruising and bleeding at the site of injection

All patients

Not known: frequency cannot be estimated from available data

Serious allergic reactions which may include:

Sudden life-threatening allergic reactions (anaphylaxis)

Swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing (angioedema)

Shortness of breath (allergic bronchospasm)

Skin rash

Hives (urticaria)

Serious skin rashes including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in association with epoetin treatment. These can appear as reddish target-like macules or circular patches often with central blisters on the trunk, skin peeling, ulcers of mouth, throat, nose, genitals and eyes and can be preceded by

fever and flu-like symptoms. Stop using DARBATITOR if you develop these symptoms and contact your doctor or seek medical attention immediately.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store DARBATITOR

Store at 2°C to 8°C. Protect from light.

Do not dilute Darbapoetin alfa injection.

Do not use if presence of any particulate matter or discolouration.

Discard any unused portion. Protect from light until administration.

9.6 Contents of the pack and other information

What DARBATITOR contains

- The active substance is Darbapoetin alfa (r-DNA origin)

The other ingredients are: Monobasic Sodium Phosphate (Monohydrate), Sodium Phosphate Dibasic Anhydrous, Sodium Chloride, Polysorbate 80 and Water for Injection.

10. Details of manufacturer

Hetero Biopharma Limited

TSIIC Formulation SEZ, Sy. No. 458 (Part), Polepally Village,

Jadcherla Mandal, Mahaboobnagar District – 509 301, Telangana State, India.

11. Details of permission or licence number with date

Mfg Lic No. 01/MN/AP/rDNA/2014/G issued on 07.05.2019.

12. Date of revision

Jul /2020

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

FOR SALE IN INDIA ONLY.

IN/DARBATITOR 25,40,60 mcg/Jul-20/03/PI