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

DARBATITOR

(Darbepoetin alfa Injection**)**

COMPOSITION

DARBATITOR 25

Each pre-filled syringe (0.42 ml) contains:
Darbepoetin alfa (r-DNA origin) 25 mcg
Monobasic Sodium phosphate (monohydrate) I.P.,
Sodium phosphate dibasic anhydrous U.S.P,
Sodium chloride I.P.,
Polysorbate 80 I.P.,
Water for Injections I.P.

DARBATITOR 40

Each pre-filled syringe (0.40 ml) contains:
Darbepoetin alfa (r-DNA origin) 40 mcg
Monobasic sodium phosphate (monohydrate) I.P.,
Sodium Phosphate Dibasic anhydrous U.S.P.,
Sodium chloride I.P.,
Polysorbate 80 I.P.,
Water for Injections I.P.

DARBATITOR 60

Each pre-filled syringe (0.30 ml) contains:
Darbepoetin alfa (r-DNA origin) ……60 mcg
Monobasic Sodium Phosphate (Monohydrate) I.P,
Sodium Phosphate Dibasic Anhydrous USP,
Sodium Chloride I.P, Polysorbate 80 I.P,
Water for Injections I.P.

DOSAGE FORM

Pre-filled syringe

INDICATIONS

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

POSOLOGY AND METHOD OF ADMINISTRATION

Darbepoetin alpha 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. Darbepoetin alpha should be administered either subcutaneously or intravenously in order to increase haemoglobin to not greater than 12 g/dl (7.5 mmol/l). Subcutaneous use is preferable in patients who are not receiving haemodialysis to avoid the puncture of peripheral veins.

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

Due to intra-patient variability, occasional individual haemoglobin values for a patient above and below the desired haemoglobin level may be observed. Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin target range of 10 g/dl (6.2 mmol/l) to 12 g/dl (7.5 mmol/l). A sustained haemoglobin level of greater than 12 g/dl (7.5 mmol/l) should be avoided; guidance for appropriate dose adjustment for when haemoglobin values exceeding 12 g/dl (7.5 mmol/l) are observed are described below. A rise in haemoglobin of greater than 2 g/dl (1.25 mmol/l) over a four week period should be avoided. If it occurs, appropriate dose adjustment should be made as provided.

Treatment with Darbepoetin alpha 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 μg/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 μg/kg once every two weeks or 1.5 μg/kg once monthly. If the increase in haemoglobin is inadequate (less than 1 g/dl (0.6 mmol/l) in four weeks) increase the dose by approximately 25%. Dose increases must not be made more frequently than once every four weeks.

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

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

Maintenance phase:

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

In patients not on dialysis, Darbepoetin alpha may continue to be administered as a single injection once weekly or once every two weeks or once monthly. For patients treated with Darbepoetin alpha once every two weeks, after the target haemoglobin has been achieved,

Darbepoetin alpha 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 mol/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.

Reported clinical studies have demonstrated that adult patients receiving r-HuEPO one, two or three times weekly may be converted to once weekly or once every other week Darbepoetin alpha. The initial weekly dose of Darbepoetin alpha (μg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 200. The initial every other week dose of Darbepoetin alpha (μg/every other week) can be determined by dividing the total cumulative dose of r-HuEPO administered over a two-week period by 200. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Darbepoetin alpha 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 reported randomised clinical trials.

Correction phase:

For patients ≥ 1 year of age, the initial dose by subcutaneous or intravenous administration is 0.45 μg/kg body weight, as a single injection once weekly. Alternatively, in patients not on dialysis, an initial dose of 0.75 μg/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 Darbepoetin alpha dosing frequency has not been studied.

Maintenance phase:
For paediatric patients ≥ 1 year of age, in the maintenance phase, Darbepoetin alpha may continue to be administered as a single injection once weekly or once every two weeks. Patients < 6 years of age may need higher doses for maintenance of haemoglobin than patients above that age. Dialysis patients converting from once weekly to once every other week dosing with Darbepoetin alpha 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, Darbepoetin alpha may be administered subcutaneously once monthly using an initial dose equal to twice the previous once every two-week dose. Reported clinical data in paediatric patients has demonstrated that patients receiving r-HuEPO two or three times weekly may be converted to once weekly Darbepoetin alpha, and those receiving r-HuEPO once weekly may be converted to once every other week Darbepoetin alpha. The initial weekly paediatric dose of Darbepoetin alpha (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. The initial every other week dose of Darbepoetin alpha (µg/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 Darbepoetin alpha 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 Darbepoetin alpha 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 Darbepoetin alpha 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 μg (6.75 μg/kg) given once every three weeks, or once weekly dosing can be given at 2.25 μg/kg body weight. If the clinical response of the patient (fatigue, haemoglobin response) is inadequate after nine weeks, further therapy may not be effective.

Darbepoetin alpha therapy should be discontinued approximately four weeks after the end of chemotherapy. Once the therapeutic objective for an individual patient has been achieved, the dose should be reduced by 25 to 50% in order to ensure that the lowest approved dose of Darbepoetin alpha is used to maintain haemoglobin at a level that controls the symptoms of anaemia. Appropriate dose titration between 500 μg, 300 μg, and 150 μg should be considered. Patients should be monitored closely, if the haemoglobin exceeds 12 g/dl (7.5 mmol/l), the dose should be reduced by approximately 25 to 50%. Treatment with Darbepoetin alpha 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
Darbepoetin alpha is administered either subcutaneously or intravenously as described in the posology. Rotate the injection sites and inject slowly to avoid discomfort at the site of injection. Darbepoetin alpha is supplied ready for use in a pre-filled syringe

CONTRAINDICATIONS
- Hypersensitivity to the active substance or to any of the expedients.
- Poorly controlled hypertension.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

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

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

Non-response to therapy with Darbepoetin should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of ESAs and should therefore be corrected. Intercurrent infections, inflammatory or traumatic episodes, occult blood loss, haemolysis, severe aluminium toxicity, underlying haematologic diseases, or bone marrow fibrosis may also compromise the erythropoietic response. A reticulocyte count should be considered as part of the evaluation. If typical causes of non-response are excluded, and the patient has reticulocytopenia, an examination of the bone marrow should be considered. If the bone marrow is consistent with PRCA, testing for anti-erythropoietin antibodies should be performed.

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

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, Darbepoetin should be withdrawn immediately and an alternative treatment considered.

If the patient has developed a severe cutaneous skin reaction such as SJS or TEN due to the use of Darbepoetin, treatment with Darbepoetin must not be restarted in this patient at any time.

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

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

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

Darbepoetin should also be used with caution in those patients with sickle cell anaemia.

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

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

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

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

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

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

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

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

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

Cancer patients

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

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

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

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

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

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

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

DRUG INTERACTION

The reported 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 is given concomitantly with any of these treatments, blood levels of these substances should be monitored and the dosage adjusted as the haemoglobin rises.

PREGNANCY AND LACTATION

Pregnancy

There are no adequate and well-controlled studies with Darbepoetin in pregnant women.

Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. No alteration of fertility was detected.

Caution should be exercised when prescribing Darbepoetin to pregnant women.

Breast-feeding

It is unknown whether Darbepoetin is excreted in human milk. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Darbepoetin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Darbepoetin has no or negligible influence on the ability to drive and use machines.

UNDESIRABLE EFFECTS
Summary of the safety profile
Identified adverse reactions associated with Darbepoetin are hypertension, stroke, thromboembolic events, convulsions, allergic reactions, rash/erythema and pure red cell aplasia (PRCA); .

Injection site pain was reported as attributable to treatment in studies where Darbepoetin was administered via subcutaneous injection. The injection site discomfort was generally mild and transient in nature and occurred predominantly after the first injection.

Tabulated list of adverse reactions
Incidence of adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Data are presented separately for CRF and cancer patients reflecting the different adverse reaction profile in these populations.

Chronic renal failure patients
In study data presented from reported controlled studies included 1,357 patients, 766 who received Darbepoetin and 591 patients who received r-HuEPO. In the Darbepoetin group, 83% were receiving dialysis and 17% were not receiving dialysis. Stroke was identified as an adverse reaction in an additional reported clinical study.

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

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

*see “Description of selected adverse reactions”

Cancer patients
Adverse reactions were determined based on pooled data from seven randomised, double-blind, placebo-controlled reported studies of Darbepoetin with a total of 2,112 patients (Darbepoetin 1,200, placebo 912). 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 reported controlled clinical studies and post-marketing experience are:

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

* see "Description of selected adverse reactions"

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 reported clinical trial data as very common in CRF patients. 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. The frequency is estimated from reported clinical trial data as uncommon in CRF patients.

Cancer patients
Hypertension has been observed in cancer patients in post-marketing experience. The frequency is estimated from reported 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 reported 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 reported 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.

OVERDOSE
The maximum amount of Darbepoetin that can be safely administered in single or multiple doses has not been determined. Therapy with Darbepoetin can result in polycythaemia if the haemoglobin is not carefully monitored and the dose appropriately adjusted. Cases of severe hypertension have been observed following overdose with Darbepoetin.

In the event of polycythaemia, Darbepoetin should be temporarily withheld. If clinically indicated, phlebotomy may be performed.

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: Anti-anaemic preparations, other anti-anaemic preparations , ATC Code: B03XA02.

Mechanism of action

Human erythropoietin is an endogenous glycoprotein hormone that is the primary regulator of erythropoiesis through specific interaction with the erythropoietin receptor on the erythroid progenitor cells in the bone marrow. The production of erythropoietin primarily occurs in and is regulated by the kidney in response to changes in tissue oxygenation. Production of endogenous erythropoietin is impaired in patients with chronic renal failure and the primary cause of their 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.

Pharmacodynamic effects

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.

Clinical efficacy and safety

Chronic renal failure patients

Patients with CRF experienced greater risks for death and serious cardiovascular events when administered ESAs to target higher versus lower haemoglobin levels (13.5 g/dl (8.4 mmol/l) versus 11.3 g/dl (7.1 mmol/l); 14 g/dl (8.7 mmol/l) versus 10 g/dl (6.2 mmol/l) in two reported clinical studies.

In a reported randomised, double-blind correction study (n = 358) comparing once every two week and once monthly dosing schedules in patients with CRF not on dialysis, darbepoetin alfa once monthly dosing was non-inferior to once every two week dosing for correcting anaemia. The median (quartile 1, quartile 3) time to achieve haemoglobin correction (≥ 10.0 g/dl and ≥ 1.0 g/dl increase from baseline) was 5 weeks for both once every two week (3, 7 weeks) and once monthly dosing (3, 9 weeks). During the evaluation period (weeks 29-33), the mean (95% CI) weekly equivalent dose was 0.20 (0.17, 0.24) μg/kg in the once every two week arm and 0.27 (0.23, 0.32) μg/kg in the once monthly arm.

In a reported randomised, double-blind, placebo-controlled study (TREAT) of 4,038 CRF patients not on dialysis with type 2 diabetes and haemoglobin levels ≤ 11 g/dl, patients received either treatment with darbepoetin alfa to target haemoglobin levels of 13 g/dl or placebo (with darbepoetin alfa rescue at haemoglobin less than 9 g/dl). The study did not meet either primary objective of demonstrating a reduction in risk for all-cause mortality or cardiovascular morbidity (darbepoetin alfa vs placebo; HR 1.05, 95% CI (0.94, 1.17)), or all-cause mortality or end stage renal disease (ESRD) (darbepoetin alfa vs placebo; HR 1.06, 95% CI (0.95, 1.19)). Analysis of the individual components of the composite endpoints showed the following HR (95% CI): death 1.05 (0.92, 1.21), congestive heart failure (CHF) 0.89 (0.74, 1.08), myocardial infarction (MI) 0.96 (0.75, 1.23), stroke 1.92 (1.38, 2.68), hospitalisation for myocardial ischaemia 0.84 (0.55, 1.27), ESRD 1.02 (0.87, 1.18).

Pooled post-hoc analyses of reported clinical studies of ESAs have been performed in chronic renal failure patients (on dialysis, not on dialysis, in diabetic and non-diabetic patients). A tendency towards increased risk estimates for all-cause mortality, cardiovascular and cerebrovascular events associated with higher cumulative ESA doses independent of the diabetes or dialysis status was observed.

Paediatric population
In a reported randomised clinical study 114 paediatric patients aged 2 to 18 with chronic kidney disease receiving or not receiving dialysis who were anaemic (haemoglobin < 10.0 g/dl) and not being treated with an ESA were administered darbepoetin alfa weekly (n = 58) or once every two weeks (n = 56) for the correction of anaemia. Haemoglobin concentrations were corrected to ≥ 10 g/dl in > 98% ($p < 0.001$) of paediatric patients administered darbepoetin alfa once weekly and 84% ($p = 0.293$) once every two weeks. At the time haemoglobin ≥ 10.0 g/dl was first achieved, the mean (SD) weight-adjusted dose was 0.48 (0.24) µg/kg (range: 0.0 to 1.7 µg/kg) weekly for the once weekly group and 0.76 (0.21) µg/kg (range: 0.3 to 1.5 µg/kg) biweekly for the once every two week group.

In a reported clinical study in 124 paediatric patients with chronic kidney disease receiving or not receiving dialysis aged 1 to 18, patients that were stable on epoetin alfa were randomised to receive either darbepoetin alfa administered once weekly (subcutaneously or intravenously) using a dose conversion ratio of 238:1 or to continue with epoetin alfa therapy at the current dose, schedule, and route of administration. The primary efficacy endpoint [change in haemoglobin between baseline and the evaluation period (week 21-28)] was comparable between the two groups. The mean haemoglobin for r-HuEPO and darbepoetin alfa at baseline was 11.1 (SD 0.7) g/dl and 11.3 (SD 0.6) g/dl, respectively. The mean haemoglobin at week 28 for r-HuEPO and darbepoetin alfa was 11.1 (SD 1.4) g/dl and 11.1 (SD 1.1) g/dl, respectively.

In a reported European observational registry study which enrolled 319 paediatric patients with chronic kidney disease (13 (4.1%) patients < 1 year of age, 83 (26.0%) patients 1-< 6 years of age, 90 (28.2%) patients 6-< 12 years of age, and 133 (41.7%) patients ≥ 12 years of age) receiving darbepoetin alfa, mean haemoglobin concentrations ranging between 11.3 and 11.5 g/dl and mean weight-adjusted darbepoetin alfa doses remained relatively constant (between 2.31 µg/kg month and 2.67 µg/kg month) over the study period for the entire study population.

In these studies, no meaningful differences were identified between the safety profile for paediatric patients and that previously reported for adult patients .

Cancer patients receiving chemotherapy
In a reported prospective, randomised double-blind, placebo-controlled study conducted in 314 lung cancer patients receiving platinum containing chemotherapy there was a significant reduction in transfusion requirements ($p < 0.001$).

Reported clinical studies have demonstrated that darbepoetin alfa had similar effectiveness when administered as a single injection either once every three weeks, once every two weeks, or weekly without any increase in total dose requirements.

The safety and effectiveness of once every three weeks dosing of Darbepoetin therapy in reducing the requirement for red blood cell transfusions in patients undergoing chemotherapy was assessed in a reported randomised, double-blind, multinational study. This study was conducted in 705 anaemic patients with non-myeloid malignancies receiving multi-cycle chemotherapy. Patients were randomised to receive Darbepoetin at 500 µg once every three weeks or 2.25 µg/kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg/kg in the once weekly group) if haemoglobin

increased by more than 1 g/dl in a 14-day period. In the once every three weeks group, 72% of patients required dose reductions. In the once weekly group, 75% of patients required dose reductions. This study supports 500 μg once every three weeks being comparable to once weekly administration with respect to the incidence of subjects receiving at least one red blood cell transfusion from week 5 to the end of treatment phase.

In a reported prospective, randomised double-blind, placebo-controlled study conducted in 344 anaemic patients with lymphoproliferative malignancies receiving chemotherapy there was a significant reduction in transfusion requirements and an improvement in haemoglobin response ($p < 0.001$). Improvement in fatigue, as measured by the Functional Assessment of Cancer Therapy-fatigue (FACT-fatigue) scale, was also observed.

Erythropoietin is a growth factor that primarily stimulates red blood cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumour cells.

Survival and tumour progression have been examined in five large controlled studies involving a total of 2,833 patients, of which four were double-blind placebo-controlled studies and one was an open-label study. Two of the studies recruited patients who were being treated with chemotherapy. The target haemoglobin concentration in two studies was > 13 g/dl; in the remaining three studies it was 12-14 g/dl. In the open-label study there was no difference in overall survival between patients treated with recombinant human erythropoietin and controls. In the four placebo-controlled studies the hazard ratios for overall survival ranged between 1.25 and 2.47 in favour of controls. These studies have shown a consistent unexplained statistically significant excess mortality in patients who have anaemia associated with various common cancers who received recombinant human erythropoietin compared to controls. Overall survival outcome in the trials could not be satisfactorily explained by differences in the incidence of thrombosis and related complications between those given recombinant human erythropoietin and those in the control group.

A systematic review has also been performed involving more than 9,000 cancer patients participating in 57 reported clinical trials. Meta-analysis of overall survival data produced a hazard ratio point estimate of 1.08 in favour of controls (95% CI: 0.99, 1.18; 42 trials and 8,167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06; 35 trials and 6,769 patients) was observed in patients treated with recombinant human erythropoietin. There is therefore consistent evidence to suggest that there may be significant harm to patients with cancer who are treated with recombinant human erythropoietin. The extent to which these outcomes might apply to the administration of recombinant human erythropoietin to patients with cancer, treated with chemotherapy to achieve haemoglobin concentrations less than 13 g/dl, is unclear because few patients with these characteristics were included in the data reviewed.

A patient-level data analysis has also been performed on more than 13,900 cancer patients (chemo-, radio-, chemoradio-, or no therapy) participating in 53 reported controlled clinical trials involving several epoetins. Meta-analysis of overall survival data produced a hazard ratio point estimate of 1.06 in favour of controls (95% CI: 1.00, 1.12; 53 trials and 13,933 patients) and for the cancer patients receiving chemotherapy, the overall survival hazard ratio was 1.04 (95% CI: 0.97, 1.11; 38 trials and 10,441 patients). Meta-analyses also

indicate consistently a significantly increased relative risk of thromboembolic events in cancer patients receiving recombinant human erythropoietin .

PHARMACOKINETIC PROPERTIES

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

Chronic renal failure patients

The pharmacokinetics of darbepoetin alfa has been studied clinically in chronic renal failure patients following intravenous and subcutaneous administration. The terminal half-life of darbepoetin alfa is 21 hours (SD 7.5) when administered intravenously. Clearance of darbepoetin alfa is 1.9 ml/hr/kg (SD 0.56) and the volume of distribution (Vss) is approximately equal to plasma volume (50 ml/kg). Bioavailability is 37% with subcutaneous administration. Following monthly administration of darbepoetin alfa, at subcutaneous doses ranging from 0.6 to 2.1 µg/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 reported clinical studies, minimal accumulation was observed with either route of administration. In reported 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 reported European clinical studies were analysed to assess the dose required to maintain haemoglobin; no difference was observed between the average weekly dose administered via the intravenous or subcutaneous routes of injection.

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

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

Cancer patients receiving chemotherapy

Following subcutaneous administration of 2.25 µg/kg to adult cancer patients a mean peak concentration of 10.6 ng/ml (SD 5.9) of darbepoetin alfa was reached at a mean time of 91 hours (SD 19.7). These parameters were consistent with dose linear pharmacokinetics over a wide dose range (0.5 to 8 µg/kg weekly and 3 to 9 µg/kg every two weeks). Pharmacokinetic parameters did not change on multiple dosing over 12 weeks (dosing every week or every two weeks). There was an expected moderate (< 2 fold) increase in

serum concentration as steady state was approached, but no unexpected accumulation upon repeated administration. A pharmacokinetic study in patients with chemotherapy-induced anaemia treated with 6.75 µg/kg darbepoetin alfa administered SC every 3 weeks in combination with chemotherapy was conducted which allowed for full characterisation of the terminal half-life. In this study, mean (SD) terminal half-life was 74 (SD 27) hours.

PRECLINICAL SAFETY DATA
In all studies in rats and dogs darbepoetin alfa produced marked increases in haemoglobin, haematocrits, red blood cell counts and reticulocytes, which correspond to the expected pharmacological effects. Adverse events at very high doses were all considered to be related to an exaggerated pharmacological effect (decreased tissue perfusion due to increased blood viscosity). These included myelofibrosis and splenic hypertrophy as well as broadening of the ECG-QRS complex in dogs but no dysrhythmia and no effect on the QT interval were observed.

Darbepoetin alfa did not reveal any genotoxic potential nor did it have any effect on the proliferation of non-haematological cells in vitro or in vivo. In the chronic toxicity studies no tumourigenic or unexpected mitogenic responses were observed in any tissue type. The carcinogenic potential of darbepoetin alfa has not been evaluated in long-term animal studies.

In studies performed in rats and rabbits no clinically relevant evidence of harmful effects with respect to pregnancy, embryonal/ foetal development, parturition or postnatal development was observed. Placental transfer was minimal. No alteration of fertility was detected.

EXPIRY DATE
Do not use later than the date of expiry.

PACKAGING INFORMATION
Darbatitor 25
1 × 0.42 ml single-dose prefilled syringe.

Darbatitor 40
1 x 0.40 ml single-dose prefilled syringe.

Darbatitor 60
1 x 0.30 ml single-dose prefilled syringe

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

MARKETED BY
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IN/DARBATITOR 25,40,60mcg/JUN-18/02/PI