

AUSTRALIAN PRODUCT INFORMATION

ARANESP® (DARBEPOETIN ALFA)

1. NAME OF THE MEDICINE

Aranesp® is the Amgen Inc. trademark for darbepoetin alfa (rch), a novel erythropoiesis stimulating protein produced by recombinant DNA technology.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ARANESP darbepoetin alfa (rch) 10 µg/0.4mL injection syringe within a pen injector

ARANESP darbepoetin alfa (rch) 15 µg/0.38mL injection syringe within a pen injector

ARANESP darbepoetin alfa (rch) 20 µg/0.5mL injection syringe within a pen injector

ARANESP darbepoetin alfa (rch) 30 µg/0.3mL injection syringe within a pen injector

ARANESP darbepoetin alfa (rch) 40 µg/0.4mL injection syringe within a pen injector

ARANESP darbepoetin alfa (rch) 50 µg/0.5mL injection syringe within a pen injector

ARANESP darbepoetin alfa (rch) 60 µg/0.3mL injection syringe within a pen injector

ARANESP darbepoetin alfa (rch) 80 µg/0.4mL injection syringe within a pen injector

ARANESP darbepoetin alfa (rch) 100 µg/0.5mL injection syringe within a pen injector

ARANESP darbepoetin alfa (rch) 150 µg/0.3mL injection syringe within a pen injector

ARANESP darbepoetin alfa (rch) 200 µg/0.4mL injection syringe within a pen injector

ARANESP darbepoetin alfa (rch) 300 µg/0.6mL injection syringe within a pen injector

ARANESP darbepoetin alfa (rch) 500 µg/1.0mL solution for injection syringe within a pen injector

ARANESP darbepoetin alfa (rch) 15 µg/0.38mL injection syringe with automatic needle guard

ARANESP darbepoetin alfa (rch) 20 µg/0.5mL injection syringe with automatic needle guard

ARANESP darbepoetin alfa (rch) 30 µg/0.3mL injection syringe with automatic needle guard

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ARANESP darbepoetin alfa (rch) 40 µg/0.4mL injection syringe with automatic needle guard

ARANESP darbepoetin alfa (rch) 50 µg/0.5mL injection syringe with automatic needle guard

ARANESP darbepoetin alfa (rch) 60 µg/0.3mL injection syringe with automatic needle guard

ARANESP darbepoetin alfa (rch) 80 µg/0.4mL injection syringe with automatic needle guard

ARANESP darbepoetin alfa (rch) 100 µg/0.5mL injection syringe with automatic needle guard

ARANESP darbepoetin alfa (rch) 150 µg/0.3mL injection syringe with automatic needle guard

ARANESP darbepoetin alfa (rch) 200 µg/0.4mL injection syringe with automatic needle guard

ARANESP darbepoetin alfa (rch) 300 µg/0.6mL injection syringe with automatic needle guard

ARANESP darbepoetin alfa (rch) 500 µg/1.0mL solution for injection syringe with automatic needle guard

ARANESP darbepoetin alfa (rch) 10 µg/0.4mL injection syringe

ARANESP darbepoetin alfa (rch) 15 µg/0.38mL injection syringe

ARANESP darbepoetin alfa (rch) 20 µg/0.5mL injection syringe

ARANESP darbepoetin alfa (rch) 30 µg/0.3mL injection syringe

ARANESP darbepoetin alfa (rch) 40 µg/0.4mL injection syringe

ARANESP darbepoetin alfa (rch) 50 µg/0.5mL injection syringe

ARANESP darbepoetin alfa (rch) 60 µg/0.3mL injection syringe

ARANESP darbepoetin alfa (rch) 80 µg/0.4mL injection syringe

ARANESP darbepoetin alfa (rch) 100 µg/0.5mL injection syringe

ARANESP darbepoetin alfa (rch) 150 µg/0.3mL injection syringe

ARANESP darbepoetin alfa (rch) 200 µg/0.4mL injection syringe

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ARANESP darbepoetin alfa (rch) 300 µg/0.6mL injection syringe

ARANESP darbepoetin alfa (rch) 500 µg/1.0mL solution for injection syringe

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Aranesp is a sterile, clear, colourless, preservative-free aqueous solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Aranesp is indicated for the treatment of anaemia associated with chronic renal failure (CRF).

Aranesp is also indicated for the treatment of anaemia and reduction of transfusion requirements in patients with non-myeloid malignancies where anaemia develops as a result of concomitantly administered chemotherapy.

4.2 Dose and method of administration

Dosage (dose and interval)

Use the lowest dose of Aranesp that will gradually increase the haemoglobin concentration to approach a target of not more than 120 g/L; the rate of haemoglobin increase should not exceed 10 g/L in any 2-week period.

Rapid increases in haemoglobin concentrations or the use of erythropoietins in subjects with normal haemoglobin concentrations, may result in an increased risk of thrombotic adverse events (see section 4.4 Special warnings and precautions for use, Cardiovascular and thrombotic events/ increased mortality).

CRF patients

For patients where intravenous (IV) access is routinely available (haemodialysis patients), administration of Aranesp by the IV route is preferable. Where IV access is not readily available (patients not yet undergoing dialysis and peritoneal dialysis patients) Aranesp may be administered as a subcutaneous (SC) injection.

The dose should be started and titrated slowly (e.g. once every 4 weeks) based on individual haemoglobin levels. The haemoglobin target, regardless of the treatment population, should not exceed 120 g/L (see section 4.2 Dose and method of administration, Dose adjustment in CRF patients). Clinical studies have shown

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interpatient response to be variable. If a patient fails to respond, or maintain a response, other aetiologies should be considered and evaluated (see section 4.4 Special warnings and precautions for use, General). Haemoglobin levels should be monitored frequently until stable. Thereafter, haemoglobin levels can be monitored less frequently. In clinical studies that were used for approval of Aranesp in patients with CRF, haemoglobin levels were measured every 1 to 2 weeks.

Dosing instructions are provided for two phases of treatment: correction of anaemia and maintenance of the target haemoglobin level. Instructions for dose adjustment and for conversion from recombinant human erythropoietin (r-HuEPO) to Aranesp are also provided.

Correction of anaemia

The initial or starting dose of Aranesp for patients on dialysis is 0.45 µg/kg body weight administered as a single SC or IV injection once weekly.

Patients not on dialysis may receive any of the following initial doses:

- 0.45 µg/kg as a single SC injection once weekly, or
- 0.75 µg/kg as a single SC injection once every 2 weeks, or
- 1.5 µg/kg as a single SC injection once-monthly

If the increase in haemoglobin is inadequate (less than 10 g/L in 4 weeks) and iron stores are adequate (see section 4.4 Special warnings and precautions for use, General), the dose of Aranesp may be increased by approximately 25%. Further increases may be made at 4-week intervals, until the desired response is attained.

Maintenance of haemoglobin concentration

For patients on dialysis, Aranesp may be dosed once weekly or once every 2 weeks at the titrated dose to maintain the target haemoglobin.

For patients not on dialysis, Aranesp may be dosed once weekly, once every 2 weeks or once monthly at the titrated dose to maintain the target haemoglobin.

Patients not on dialysis receiving Aranesp once every 2 weeks may be dosed once monthly using twice the once every 2-week dose. Thereafter, the monthly dose should be titrated as necessary to maintain the haemoglobin target. If a dose adjustment is required to maintain a target haemoglobin, the individual dose may be adjusted at 4-week intervals until the appropriate haemoglobin level is achieved (see section 4.2 Dose and method of administration, Dose adjustment in CRF patients).

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Dose changes in the maintenance phase of treatment should not be made more frequently than every 2 weeks.

When changing the route of administration, the same dose should be used and the haemoglobin monitored so that the appropriate Aranesp dose adjustments can be made to keep the haemoglobin at a target not to exceed 120 g/L. Data from 809 patients receiving Aranesp in Australian and 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 IV and SC routes of injection.

Conversion from recombinant human erythropoietin to Aranesp

Due to its longer serum half-life, Aranesp can be administered less frequently than r-HuEPO. Clinical experience has shown that patients receiving r-HuEPO 2 or 3 times weekly may change to once weekly Aranesp. Those receiving r-HuEPO once weekly may change to Aranesp administered once every 2 weeks. The substitution of Aranesp for r-HuEPO should be based on the patient's r-HuEPO dose at the time of substitution, and the same route of administration should be used. The initial SC dose of Aranesp ($\mu\text{g}/\text{week}$) can be determined by dividing the total weekly SC dose of r-HuEPO (U/week) by 200, while the initial IV dose can be determined by dividing the total weekly IV dose of r-HuEPO (U/week) by 240. Because of individual variability, doses should be titrated as described above to maintain the haemoglobin at the desired concentration.

Patients with non-myeloid malignancies receiving chemotherapy

Treatment should not be commenced unless haemoglobin falls below 100 – 110 g/L. The recommended initial dose is 500 μg or 6.75 $\mu\text{g}/\text{kg}$ body weight given once every 3 weeks as a single SC injection. If the clinical response of the patient (fatigue, haemoglobin response) is inadequate after nine weeks, further therapy may not be effective. Alternatively, once-weekly SC dosing can be given at 2.25 $\mu\text{g}/\text{kg}$ body weight. The aim of treatment is to increase haemoglobin concentration to a target not to exceed 120 g/L and to reduce the requirement for blood transfusions. The therapy should be continued for approximately 4 weeks after the end of chemotherapy or until haemoglobin concentrations approach 120 g/L.

Method of administration

Aranesp may be administered by either a pre-filled syringe, pre-filled syringe with automatic needle guard or pre-filled pen (SureClick®).

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Aranesp may be administered SC by a patient or caregiver after being trained by a doctor, nurse or pharmacist.

Do not shake Aranesp. Prolonged vigorous shaking may denature any protein, rendering it biologically inactive.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration. Do not use any products exhibiting particulate matter or discolouration.

Do not dilute or administer Aranesp in conjunction with other drug solutions.

Aranesp contains no antimicrobial agent. Aranesp is for single use in one patient only. Discard any residue.

Allow Aranesp to reach room temperature before injecting.

The Aranesp pre-filled pen (SureClick) delivers the complete dose by SC administration.

Dosage adjustment

Dose adjustment in CRF patients

The dose should be adjusted for each patient to achieve and maintain a target haemoglobin not to exceed 120 g/L. Dose adjustment instructions should be followed to achieve and maintain a target haemoglobin or in response to an excessive rate of rise of haemoglobin.

If the haemoglobin is increasing and approaching 120 g/L, 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 a dose approximately 25% below the previous dose.

If the rise in haemoglobin is more than 10 g/L in 2 weeks, reduce the dose by 25%.

Dose adjustment in cancer patients

If the haemoglobin approaches 120 g/L, the dose should be reduced by 25 to 50%. For both once weekly and once every 3-week dosing schedules, if the haemoglobin exceeds 120 g/L treatment should be temporarily withheld until the haemoglobin decreases to approximately 110 g/L, at which point therapy should be re-initiated at 25 to 50% below the previous dose.

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If haemoglobin increases by more than 10 g/L in a 2-week period, the dose should be reduced by 25 to 50%.

For patients receiving Aranesp on a weekly basis, if the increase in haemoglobin is inadequate (less than 10 g/L after approximately 1 month of therapy), or if the response is not satisfactory in terms of reducing red blood cell (RBC) transfusion requirements, the dose should be doubled to 4.5 µg/kg given once weekly.

4.3 Contraindications

Aranesp is contraindicated in patients with:

1. Uncontrolled hypertension.
2. Known sensitivity to products derived from mammalian cells.
3. Known hypersensitivity to darbepoetin alfa or any of the excipients found in Aranesp.

4.4 Special warnings and precautions for use

Cardiovascular and thrombotic events/ increased mortality

Cardiovascular and thrombotic events such as myocardial ischaemia and infarction, cerebrovascular haemorrhage and infarction, transient ischaemic attacks, deep venous thrombosis, arterial thrombosis, pulmonary emboli, retinal thrombosis and haemodialysis graft occlusion have been reported in patients receiving erythropoiesis stimulating agents (ESAs) such as Aranesp.

ESAs have been associated with an increased risk of death, serious cardiovascular events or stroke in controlled clinical trials when administered to target a haemoglobin of greater than 120 g/L. There was an increased risk of serious arterial and venous thromboembolic events, including myocardial infarction, stroke, congestive heart failure, and haemodialysis graft occlusion. A rate of haemoglobin rise of greater than 10 g/L over 2 weeks may also contribute to these risks.

To reduce cardiovascular risks, use the lowest dose of Aranesp that will gradually increase the haemoglobin concentration. The haemoglobin concentration should aim not to exceed a target of 120 g/L; the rate of haemoglobin increase should not exceed 10 g/L in any 2-week period (see section 4.2 Dose and method of administration).

CRF patients with relative hyporesponsiveness to ESAs may be at increased risk for mortality and cardiovascular events. These patients should be evaluated for treatable

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conditions and caution should be used when increasing the dose (see section 4.4 Special warnings and precautions for use, General).

In a randomised prospective trial, 1,432 anaemic CRF patients who were not undergoing dialysis were assigned to epoetin alfa treatment targeting a maintenance haemoglobin concentration of 135 g/L or 113 g/L. A major cardiovascular event (death, myocardial infarction, stroke, or hospitalisation for congestive heart failure) occurred among 125 (18%) of the 715 patients in the higher haemoglobin group compared to 97 (14%) among the 717 patients in the lower haemoglobin group (HR 1.3, 95% CI: 1.0, 1.7, $p = 0.03$).

Increased risk for serious cardiovascular events was also reported from a randomised, prospective trial of 1,265 haemodialysis patients with clinically evident cardiac disease (ischaemic heart disease or congestive heart failure). In this trial, patients were assigned to epoetin alfa treatment targeted to a maintenance haemoglobin of either 140 ± 10 g/L or 100 ± 10 g/L. Higher mortality (35% versus 29%) was observed in the 634 patients randomised to a target haemoglobin of 140 g/L than in the 631 patients assigned a target haemoglobin of 100 g/L. The reason for the increased mortality observed in this study is unknown; however, the incidence of nonfatal myocardial infarction, vascular access thrombosis, and other thrombotic events was also higher in the group randomised to a target haemoglobin of 140 g/L.

In a randomised, double-blind, placebo-controlled study of 4,038 patients called TREAT, there was an increased risk of stroke (HR 1.92, 95% CI: 1.38, 2.68) when Aranesp was administered to anaemic patients with type 2 diabetes and CRF not on dialysis to target a haemoglobin level of 130 g/L compared with placebo-treated patients who received Aranesp when their haemoglobin levels were less than 90 g/L.

In a post hoc subgroup analysis of TREAT, more deaths from any cause were observed in those patients who indicated a prior history of malignancy and were treated with Aranesp to target a haemoglobin level of 130 g/L (60 deaths out of 188 patients randomised to Aranesp versus 37 deaths out of 160 patients randomised to placebo; HR: 1.38, 95% CI: 0.91, 2.07).

An increased incidence of thrombotic events has also been observed in patients with cancer treated with ESAs such as Aranesp (see section 4.8 Adverse effects (Undesirable effects), Adverse events in cancer patients, Thrombotic events in cancer patients).

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In a randomised controlled study (referred to as the 'BEST' study) with another ESA in 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 an ESA was administered to prevent anaemia (maintain haemoglobin levels between 120 and 140 g/L or haematocrit between 36% and 42%). The trial was terminated prematurely when interim results demonstrated that a higher mortality at 4 months (8.7% versus 3.4%) and a higher rate of fatal thrombotic events (1.1% versus 0.2%) in the first 4 months of the study were observed 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% versus 76%; HR 1.37, 95% CI: 1.07, 1.75; $p = 0.012$).

A systematic review of 57 randomised controlled trials (including the BEST and ENHANCE studies) evaluating 9,353 patients with cancer compared ESAs plus RBC transfusion with RBC transfusion alone for prophylaxis or treatment of anaemia in cancer patients with or without concurrent antineoplastic therapy. 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 ESA- treated patients. An overall survival hazard ratio of 1.08 (95% CI: 0.99, 1.18; 42 trials and 8,167 patients) was observed in ESA-treated patients.

Growth factor potential/increased tumour progression

Aranesp is a growth factor that primarily stimulates RBC production. Like all growth factors, there is a theoretical concern that Aranesp could act as a growth factor for any tumour type, particularly myeloid malignancies.

ESAs have been associated with shortened time to tumour progression in patients with advanced head and neck cancer receiving radiation therapy when administered to a haemoglobin between 140 to 155 g/L. Aranesp should only be used to treat cancer patients with anaemia where the anaemia has arisen as a result of concomitantly administered chemotherapy.

The ENHANCE study was a randomised controlled study in 351 head and neck cancer patients where epoetin beta or placebo was administered to achieve target haemoglobins of 140 and 150 g/L for women and men, respectively. Locoregional progression-free survival was significantly shorter in patients receiving epoetin beta, hazard ratio 1.62 (95% CI: 1.22, 2.14; $p = 0.0008$) with a median of 406 days epoetin beta versus 745 days placebo.

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The DAHANCA 10 study, conducted in 522 patients with primary squamous cell carcinoma of the head and neck receiving radiation therapy were randomised to Aranesp or placebo. An interim analysis in 484 patients demonstrated a 10% increase in locoregional failure rate among Aranesp-treated patients ($p = 0.01$). At the time of study termination, there was a trend toward worse survival in the Aranesp-treated arm ($p = 0.08$).

ESAs have been associated with shortened survival in patients with metastatic breast cancer receiving chemotherapy when administered to a target haemoglobin of greater than 120 g/L.

The BEST study was previously described (see section 4.4 Special warnings and precautions for use, Cardiovascular and thrombotic events/ increased mortality). Mortality at 4 months (8.7% versus 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 progressive disease. Investigator assessed time to tumour progression was not different between the two groups.

Use in cancer patients

ESAs have been associated with an increased risk of death when administered to a haemoglobin target of 120 to 140 g/L in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. Aranesp is not indicated for this population. Aranesp should only be used to treat cancer patients with anaemia where the anaemia has arisen as a result of concomitantly administered chemotherapy.

In a Phase 3, double-blind, randomised (Aranesp versus placebo), 16-week study in 989 anaemic 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. In addition, there were more deaths in the Aranesp treatment group [26% (136/515)] than the placebo group [20% (94/470)] at 16 weeks (completion of treatment phase). With a median survival follow up of 4.3 months, the absolute number of deaths was greater in the Aranesp treatment group [49% (250/515)] compared with the placebo group [46% (216/470)]; HR 1.29, 95% CI: 1.08, 1.55].

In a Phase 3, multicentre, randomised (epoetin alfa versus placebo), double-blind study, patients with advanced non-small cell lung cancer unsuitable for curative therapy were

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treated with epoetin alfa targeting haemoglobin levels between 120 and 140 g/L. Following an interim analysis of 70 of 300 patients planned, a significant difference in median survival in favour of patients in the placebo group was observed (63 versus 129 days; HR 1.84; p = 0.04).

Hypertension

Patients with uncontrolled hypertension should not be treated with Aranesp; blood pressure should be controlled adequately before initiation of therapy. Blood pressure may rise during treatment of anaemia with Aranesp. Hypertensive encephalopathy and seizures have been observed in patients with CRF treated with Aranesp or epoetin alfa.

Special care should be taken to closely monitor and control blood pressure in patients treated with Aranesp. During Aranesp therapy patients should be advised of the importance of compliance with antihypertensive therapy and dietary/fluid restriction. If blood pressure is difficult to control after initiation of appropriate antihypertensive measures, the dose of Aranesp should be reduced or temporarily withheld until haemoglobin begins to decrease (see section 4.2 Dose and method of administration). A clinically significant change in haemoglobin may occur, but may not be observed for several weeks.

Pure red cell aplasia

Pure red cell aplasia (PRCA) in association with neutralising antibodies to native erythropoietin has been observed in patients treated with ESAs, including Aranesp. This has been reported predominantly in patients with CRF and in patients with hepatitis C treated with interferon and ribavirin. Most cases have been associated with SC administration of ESAs.

Any patient with loss of response to Aranesp should be investigated for the typical causes of loss of effect (see section 4.4 Special warnings and precautions for use, General). Aranesp should be discontinued in any patient with evidence of PRCA and the patient evaluated for the presence of binding and neutralising antibodies to Aranesp, native erythropoietin, and any other ESA administered to the patient. In patients with PRCA secondary to neutralising antibodies to any ESA, Aranesp should not be administered. Patients should not be switched to other ESA as antibodies may cross-react with other erythropoietins.

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Convulsions

Aranesp should be used with caution in patients with a history of convulsions. Cases of convulsions have been very rarely reported in patients receiving Aranesp.

General

In order to ensure effective erythropoiesis, iron status should be evaluated for all patients before and during treatment, as the majority of patients will eventually require supplemental iron therapy. As per CARI Guidelines (Caring for Australians with Renal Impairment), supplemental iron therapy is recommended for all CRF patients whose serum ferritin is below 100 µg/L or serum transferrin saturation is below 20%.

A lack of response or failure to maintain a haemoglobin response with Aranesp doses within the recommended dosing range should prompt a search for causative factors. Deficiencies of folic acid or vitamin B₁₂ should be excluded or corrected. Intercurrent infections, inflammatory or malignant processes, osteofibrosis cystica, occult blood loss, haemolysis, severe aluminium toxicity or bone marrow fibrosis may compromise an 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 and a bone marrow biopsy demonstrates pure red cell aplasia, testing for anti-erythropoietin antibodies should be conducted. If patients do not respond to Aranesp and no causal factor can be found consider discontinuing Aranesp.

The safety and efficacy of Aranesp therapy have not been established in patients with underlying haematologic diseases (e.g. haemolytic anaemia, sickle cell anaemia, thalassaemia and porphyria).

Severe cutaneous reactions

Blistering and skin exfoliation reactions including Erythema multiforme and Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN), have been reported in patients treated with Aranesp in the post-marketing environment. Discontinue Aranesp therapy immediately if a severe cutaneous reaction, such as SJS/TEN, is suspected.

Allergic reactions

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, dyspnoea, skin rash and urticaria associated with Aranesp. Symptoms have recurred with rechallenge, suggesting a causal relationship exists in some cases.

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Precautions should be taken when administering Aranesp in case allergic or other untoward reactions occur. If a serious allergic or anaphylactic reaction occurs, Aranesp should be immediately discontinued and appropriate therapy administered.

Use in the elderly

Refer to section 5.1 Pharmacodynamic properties, Clinical trials, Geriatric use.

Paediatric use

The safety and efficacy of Aranesp in paediatric patients have not been established.

Effects on laboratory tests

In clinical studies, no treatment effect was observed for biochemistry parameters. Generally, values remained within the expected range for patients with CRF. Changes in haematology (red blood cells, reticulocytes) were consistent with the pharmacologic effects of Aranesp.

4.5 Interaction with other medicines and other forms of interaction

The theoretical risk of any drug interaction is low due to the clearance and mechanism of action of Aranesp (see sections 5.1 Pharmacodynamic properties and 5.2 Pharmacokinetic properties). No evidence of drug interactions with Aranesp was observed during the course of clinical studies.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No adverse effects on fertility were observed in male and female rats at IV darbepoetin alfa doses of up to 10 µg/kg 3 times weekly. Systemic exposure (plasma AUC times number of doses/week) at the highest dose was about 4 times greater than that in humans at the recommended initial SC dose of 2.25 µg/kg in cancer patients. An increase in post implantation loss was seen at darbepoetin alfa doses of 0.5 µg/kg/day and higher, but this was considered to be associated with polycythaemia in the dams and is therefore unlikely to be of clinical relevance.

Use in pregnancy

Pregnancy category: B3

Reproductive studies in rats showed no significant placental transfer of darbepoetin alfa. Studies in pregnant rats and rabbits showed no evidence of direct embryotoxic, fetotoxic

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or teratogenic properties of darbepoetin alfa at IV doses of up to 20 µg/kg/day. Systemic exposure (AUC/dose) at the highest dose was about 4 times (rats) and 20 times (rabbits) than that in humans at the recommended initial SC dose of 2.25 µg/kg in cancer patients. Reductions in foetal weights were observed in both species and were probably associated with polycythaemia in the dams. IV injection of Aranesp to female rats every other day from day 6 of gestation through day 23 of lactation at doses of 2.5 µg/kg/dose and higher resulted in offspring (F1 generation) with decreased body weights, which correlated with a low incidence of deaths, as well as delayed eye opening and delayed preputial separation. No adverse effects were seen in the F2 offspring.

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

No studies have been conducted in pregnant women. Aranesp should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in lactation

It is not known whether darbepoetin alfa is excreted in human milk, although many drugs are excreted in human milk. In a reproductive study in rats, IV administration of darbepoetin alfa during gestation and lactation at doses of up to 10 µg/kg/day caused decreases in pup viability during lactation and delays in pup development, in addition to reductions in pup birth weights. Although these effects were probably due to polycythaemia and associated toxicity in the dams, caution should be exercised when Aranesp is administered to a breastfeeding woman.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (Undesirable effects)

Adverse events in CRF patients

Data from clinical studies

Aranesp was well tolerated in clinical studies involving 1,578 patients, with an exposure of 942 patient years. The adverse events reported are typical sequelae of CRF and are

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not necessarily attributable to Aranesp therapy. The adverse events reported in $\geq 5\%$ of patients treated with Aranesp compared with r-HuEPO are shown in Table 1. Adverse events reported in $< 5\%$ of patients treated with Aranesp that are considered to be of interest are shown in Table 2. The incidence of deaths was 7% in the Aranesp-treated patients and 6% in the r-HuEPO-treated patients.

The data described in Table 3 reflect exposure to Aranesp and placebo in 4,023 patients who received at least one dose of investigational product from the TREAT study; a randomised placebo controlled clinical study in adult CRF patients not on dialysis with type 2 diabetes (see section 4.4 Special warnings and precautions for use).

Table 1. Adverse events reported in $\geq 5\%$ of CRF patients on Aranesp compared with r-HuEPO

Body system and preferred terms	Percent of patients reporting events	
	Aranesp n = 1,578	r-HuEPO n = 591
Application site		
Injection site pain	7	1
Body as a whole		
Oedema peripheral	10	17
Fatigue	9	11
Fever	9	9
Pain chest	6	9
Access haemorrhage	6	8
Influenza-like symptoms	6	8
Fluid overload	6	8
Access infection	6	6
Cardiovascular		
Hypertension	23	26
Hypotension	22	25
Thrombosis vascular access	8	14
CNS / PNS		
Headache	16	18
Dizziness	8	15
Gastrointestinal		
Diarrhoea	15	21
Vomiting	15	20

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Body system and preferred terms	Percent of patients reporting events	
	Aranesp n = 1,578	r-HuEPO n = 591
Nausea	14	24
Pain abdominal	12	17
Constipation	5	8
Musculo-skeletal		
Myalgia	20	27
Arthralgia	11	13
Pain limb	10	16
Pain back	8	12
Respiratory		
Infection upper respiratory	14	23
Dyspnoea	12	18
Cough	10	10
Bronchitis	6	5
Skin and appendages		
Pruritus	8	7

Table 2. Adverse events of interest reported in < 5% of CRF patients treated with Aranesp

Adverse event	Percent of patients reporting events	
	Aranesp n = 1,578	r-HuEPO n = 591
CVA / TIA [‡]	1	1
Convulsions	1	2
Myocardial infarction	2	2

[‡] Cerebrovascular accident / Transient ischaemic attack

Treatment-related events were defined as those occurring in > 0.5% of patients treated with Aranesp (n = 1,598) and / or occurring in ≥ 0.2% compared to r-HuEPO (n = 600).

Subject incidence

1 to 10% hypertension, injection site pain, headache, thrombosis vascular access

<1% fatigue, anaemia, pruritus, dizziness, hypotension, nausea, arrhythmia, influenza-like symptoms, somnolence, dyspnoea, pain chest, convulsions, pain abdominal, epistaxis.

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Thrombotic events in CRF patients

Vascular access thrombosis occurred in CRF clinical studies at an annualised rate of 0.19 events per patient year of Aranesp therapy and 0.40 events per patient year of r-HuEPO. Rates of thrombotic events (e.g. vascular access thrombosis, venous thrombosis and pulmonary emboli) with Aranesp therapy were similar to those observed in r-HuEPO therapy in these studies.

Table 3. Adverse reactions occurring in adult patients not on dialysis with type 2 diabetes (TREAT) with an incidence of $\geq 5\%$ in the Aranesp group and exceeding the incidence in the placebo group by $\geq 1\%$.

Adverse Reaction	Percent of patient adverse reaction reports	
	Aranesp Group n = 2,004	Placebo Group n = 2,019
Hypertension	18%	16%
Renal failure chronic	15%	13%
Urinary tract infection	15%	14%
Hypoglycaemia	14%	13%
Dizziness	12%	10%
Nasopharyngitis	11%	9%
Headache	10%	8%
Fall	8%	7%
Cellulitis	6%	5%
Hypotension	6%	5%
Sinusitis	6%	5%
Contusion	6%	5%
Rash	6%	5%
Skin ulcer	5%	4%

Adverse events in cancer patients

Data from clinical studies

The Aranesp clinical program included evaluation of a total of 1,087 patients with cancer receiving chemotherapy in double-blind, placebo-controlled or open-label, active controlled (r-HuEPO) studies of up to 6 months duration. Death, primarily due to disease progression, occurred on study in 9% of Aranesp, 10% of placebo, and 13% of r-HuEPO subjects. Common adverse events reported by the treating physicians as severe are shown in Table 4.

Table 4. Common adverse events in cancer patients reported as severe by the treating physicians

Adverse event	Percent of reports		
	Aranesp n = 781	r-HuEPO n = 85	Placebo n = 221
Fatigue	6	4	3
Dyspnoea	4	6	6
Asthenia	4	4	3
Granulocytopenia	4	4	4

The data in Table 5 reflect the adverse events reported in at least 5% of cancer patients treated with Aranesp and receiving concomitant chemotherapy in these controlled studies. In general, adverse experiences reported in clinical trials with Aranesp in patients with cancer receiving chemotherapy were consistent with the underlying disease and its treatment with chemotherapy.

Table 5. Adverse events reported in > 5% of cancer patients on Aranesp compared with r-HuEPO and placebo

Body system and preferred terms	Percent of reports		
	Aranesp n = 781	r-HuEPO n = 85	Placebo n = 221
Body as a whole			
Fatigue	32	29	30
Fever	19	21	16
Oedema peripheral	15	18	8
Asthenia	16	12	15
Pain chest (non-cardiac)	10	11	14
Pain	8	13	5
Metastatic neoplasm	5	6	6
Oedema	5	0	1
CNS / PNS			
Dizziness	14	13	8
Headache	12	13	9
Insomnia	11	15	7
Paraesthesia	8	6	7
Hypoesthesia	7	8	4
Gastrointestinal			
Nausea	38	34	37

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Body system and preferred terms	Percent of reports		
	Aranesp n = 781	r-HuEPO n = 85	Placebo n = 221
Vomiting	27	16	28
Diarrhoea	20	26	12
Constipation	19	16	16
Anorexia	16	15	17
Pain abdominal	16	21	12
Dyspepsia	6	8	4
Haematological			
Granulocytopenia	9	7	11
Musculo-skeletal			
Pain back	14	16	14
Arthralgia	13	20	6
Pain limb	11	20	7
Myalgia	8	8	5
Pain skeletal	8	12	10
Psychiatric			
Depression	7	8	4
Anxiety	6	9	9
Respiratory			
Dyspnoea	20	20	23
Cough	8	13	13
Infection upper respiratory	8	8	7
Sore throat	6	6	5
Skin and appendages			
Alopecia	8	7	7
Rash	7	9	3

Clinically significant adverse reactions occurring in < 1% of cancer patients treated with Aranesp include: injection site reaction, headache, myalgia, arthralgia and thromboembolic events.

In clinical trials of Aranesp (n = 873) versus placebo (n = 221), one adverse reaction was reported in ≥1% of cancer patients: Injection site pain (Aranesp 4% versus placebo 3%).

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Thrombotic events in cancer patients

In cancer patients, the incidence of thrombotic events was 6% for Aranesp, 5% for r-HuEPO and 4% for placebo. The following events were reported more frequently in Aranesp-treated patients than in placebo controls, but at a rate comparable to r-HuEPO: pulmonary embolism, thromboembolism, thrombosis and thrombophlebitis (deep and/or superficial).

Adverse events, all patients

Post-marketing experience

Cases of convulsions have been very rarely reported in patients receiving Aranesp.

Rarely, serious allergic reactions have been reported with Aranesp (see section 4.4 Special warnings and precautions for use).

In patients treated with Aranesp the following skin and SC tissue adverse reactions have been reported: blistering, skin exfoliation, Erythema multiforme, SJS/TEN.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity.

Radioimmuno-precipitation (RIP) assays were performed on sera from 1,534 CRF patients and 833 cancer patients treated with Aranesp in clinical studies. Antibodies were not detected in the CRF patients; however reactivity, not considered antibody-related was detected in 3 cancer patients. The patients responded to Aranesp therapy and there was no evidence of PRCA.

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Antibody positivity in an assay may also be influenced by sample handling, timing of sample collection, concomitant medications and underlying disease. Therefore, comparison of the incidence of antibodies to Aranesp with the incidence of antibodies to other products may be misleading.

Cases of PRCA associated with neutralising antibodies to erythropoietin have been reported in patients receiving Aranesp (see section 4.4 Special warnings and precautions for use, Pure red cell aplasia).

Reporting of suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal

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product. Healthcare professionals are asked to report any suspected adverse reactions at <https://www.tga.gov.au/reporting-problems>.

4.9 Overdose

The maximum amount of Aranesp that can be safely administered in single or multiple doses has not been determined. Doses over 3.0 µg/kg/week for up to 28 weeks have been administered to CRF patients without any direct toxic effects of Aranesp itself. Doses up to 8.0 µg/kg/week and 15.0 µg/kg/3 weeks have been safely administered to cancer patients for up to 22 weeks.

Aranesp 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 Aranesp. If the suggested haemoglobin target range is exceeded, Aranesp should be reduced or temporarily withheld until the haemoglobin returns to the suggested target range. If withheld, Aranesp therapy may then be resumed using a lower dose (see section 4.2 Dose and method of administration). If clinically indicated, phlebotomy may be performed.

For advice on the management of overdose contact the Poisons Information Centre on 131126.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Erythropoietin is a glycoprotein that is the primary regulator of erythropoiesis. The production of erythropoietin primarily occurs in the kidney and is regulated in response to changes in tissue oxygenation. Endogenous erythropoietin production is impaired in patients with CRF and erythropoietin deficiency is the primary cause of their anaemia.

Erythropoietin acts through specific interaction with the erythropoietin receptor on erythroid progenitor cells in the bone marrow. Using a panel of human tissues neither darbepoetin alfa nor r-HuEPO (or their desialylated forms) bound to human tissues other than those expressing the erythropoietin receptor.

Aranesp has been shown to stimulate erythropoiesis in anaemic CRF and cancer patients, resulting in the correction and maintenance of haemoglobin. Treatment of

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anaemia of CRF and cancer has been associated with a reduction in RBC transfusions and improved quality of life.

In patients with cancer receiving concomitant chemotherapy, the aetiology of anaemia is multifactorial, with erythropoietin deficiency and a blunted response of erythroid progenitor cells to endogenous erythropoietin contributing significantly towards their anaemia.

Due to its increased sialic acid-containing carbohydrate content, Aranesp has an approximately 3-fold longer terminal half-life than erythropoietin and consequently a greater *in vivo* biologic activity when administered by either the SC or IV route.

In cancer patients with anaemia (mean \pm sd haemoglobin 99 ± 9 g/L), a range of weekly SC doses of Aranesp from 0.5 to 8.0 μ g/kg were assessed, beginning on day 1 of chemotherapy (before starting chemotherapy) and continuing for 12 weeks. Data from these studies indicate that there is a dose relationship with respect to haemoglobin response. The minimally effective starting dose with respect to reducing transfusion requirements was 1.5 μ g/kg/week with a plateau observed at 4.5 μ g/kg/week.

Preclinical experience

Aranesp undergoes extensive metabolism, with less than 2% of intact Aranesp being excreted renally in rats, while degradation products are recovered in the urine (57% dose) and faeces (24% dose). Metabolism of Aranesp may involve desialylation by blood/tissue sialidases, with subsequent rapid removal of the desialylated form by hepatic receptors, and/or reuptake via bone marrow cells.

Clinical trials

Clinical experience in CRF patients

Ten clinical studies were conducted, involving SC and IV administration of Aranesp to a total of 1,578 adult CRF patients with an exposure of 942 patient years. Response to Aranesp was consistent across all studies. The time to reach the target haemoglobin is a function of the baseline haemoglobin and the rate of haemoglobin rise. The rate of increase in haemoglobin is dependent upon the dose of Aranesp administered and individual patient variation.

Maintenance in CRF patients

Aranesp was at least equivalent to r-HuEPO in the maintenance of a target haemoglobin (haemoglobin between 90 to 130 g/L and between -10 and +15 g/L of baseline) in 2 trials

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in which adult dialysis patients were randomised to either stay on r-HuEPO or switch to Aranesp.

One trial evaluated 224 Aranesp-treated patients and 112 r-HuEPO-treated patients. The median Aranesp dose was 30 µg/week and the median r-HuEPO dose was 6,000 U/week. The drugs were administered either IV or SC at frequencies varying from 3 times weekly to once every 2 weeks. Ninety-seven percent of patients in the Aranesp group received their treatment at a lower frequency than they had previously received r-HuEPO, in most cases once weekly instead of 2 to 3 times weekly. The mean difference for change in haemoglobin from baseline (Aranesp minus r-HuEPO) was 0.3 g/L (95% confidence interval [CI]: -1.6, 2.1).

In the second trial, 121 Aranesp-treated patients and 240 r-HuEPO-treated patients were evaluated. Both drugs were administered IV, Aranesp once weekly and r-HuEPO 3 times weekly. The median Aranesp dose was 38 µg/week and the median r-HuEPO dose 9,900 U/week. The mean difference for change in haemoglobin from baseline (Aranesp minus r-HuEPO) was 1.6 g/L (95% CI: -0.8, 3.3).

There were no significant differences between the drugs in the proportion of patients with unstable haemoglobin and proportion receiving blood transfusions, in either trial.

Clinical studies in CRF patients not on dialysis have demonstrated that Aranesp has similar effectiveness when administered as a single SC monthly injection in patients stabilised on once every 2-week SC dosing, without any increase in total dose requirements.

Correction of anaemia in CRF patients

In a trial in adult predialysis CRF patients with anaemia (haemoglobin concentration < 110 g/L), Aranesp produced a similar response to r-HuEPO with 87% (95% CI: 80, 92) of Aranesp-treated patients (n = 129) and 86% (95% CI: 71, 95) of r-HuEPO-treated patients (n = 37) achieving the haemoglobin target (> 110 g/L and > 10 g/L increase from baseline) after 16 weeks. The drugs were administered by the SC route. The starting dose of Aranesp was 0.45 µg/kg once weekly (approximately equivalent to 90 U/kg of r-HuEPO weekly). The starting dose of r-HuEPO was 50 U/kg twice weekly (100 U/kg total weekly dose). The doses were adjusted in ± 25% increments at 2 to 4 week intervals as required. The median time to response was 7 weeks in each group and the median doses at response were similar to the starting doses, 0.46 µg/kg/week for

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Aranesp and 100 U/kg/week for r-HuEPO. The median dose after 16 weeks of treatment was 0.45 µg/kg/week for Aranesp and 100 U/kg/week for r-HuEPO.

In a second trial, in adult dialysis CRF patients with anaemia (haemoglobin < 100 g/L), r-HuEPO was started at a higher dose than Aranesp based on protein mass, 50 U/kg 3 times weekly (150 U/kg total weekly dose) compared with 0.45 µg/kg once weekly (approximately equivalent to 90 U/kg of r-HuEPO weekly). The drugs were administered either IV or SC. A similar regime of dosage adjustments and a similar haemoglobin target were employed to the previous trial. Of patients receiving at least one dose of drug, 95% (95% CI: 77, 100) of r-HuEPO-treated patients (n = 22) and 71% (95% CI: 59, 82) of Aranesp-treated patients (n = 70) reached the haemoglobin target by 20 weeks. The median time to response was 8 weeks in the r-HuEPO group and 9 weeks in the Aranesp group and the median doses at response were 150 U/kg/week and 0.55 µg/kg/week, respectively. The median dose after 20 weeks of treatment was 0.56 µg/kg/week for Aranesp and 150 U/kg/week for r-HuEPO.

A randomised, double-blind non-inferiority (non-inferiority margin – 5 g/L) correction study (n = 358) compared Aranesp once every 2 weeks SC and once monthly SC dosing schedules in CRF patients with anaemia not on dialysis. The initial Aranesp dose for once every 2 weeks and once monthly was 0.75 µg/kg and 1.5 µg/kg respectively. Dose adjustments were monthly, if required to correct and maintain a haemoglobin level within the target 100-120 g/L. Aranesp once monthly dosing was non-inferior to once every 2-week dosing for correcting anaemia. The median (Q1, Q3) time to achieve haemoglobin correction (≥ 100 g/L and ≥ 10 g/L increase from baseline) was 5 weeks for both once every 2 weeks (3, 7 weeks) and once monthly dosing (3, 9 weeks). During the evaluation period (weeks 29-33), the median (Q1, Q3) weekly equivalent dose was 0.23 (0.14, 0.36) µg/kg in the once every 2-week arm and 0.30 (0.18, 0.51) µg/kg in the once monthly arm.

Treatment of anaemia in cancer patients receiving chemotherapy

A randomised, double-blind, placebo-controlled, parallel-group trial was conducted in anaemic patients with lung cancer receiving multi-cycle platinum-containing chemotherapy. Randomisation was stratified by tumour type (small cell, non-small cell) and region (Australia, Canada, Central and Eastern Europe, Western Europe). The starting dose was 2.25 µg/kg/week as a single SC injection commencing on day 1 prior to administration of chemotherapy. The dose could be increased after 6 weeks up to

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4.5 µg/kg/week if patients failed to achieve an increase in haemoglobin of > 10 g/L. The duration of treatment was 12 weeks.

Efficacy was determined by a reduction in the proportion of patients who were transfused over the 12-week treatment period. A significantly lower proportion of patients in the Aranesp arm, 26% (95% CI: 20, 33) required transfusion compared to 60% (95% CI: 52, 68) in the placebo arm (Kaplan-Meier estimate of proportion; $p < 0.001$ by Cochran - Mantel - Haenszel test) (see Table 6). There was a trend in favour of Aranesp in FACT/F, a fatigue-related quality of life score.

Table 6. Trial of Aranesp in anaemia associated with chemotherapy (Modified intention-to-treat, weighted by tumour type and region)

Endpoint	Aranesp	Placebo
Number of patients		
Randomised	159	161
Modified ITT	156	158
No. of subjects transfused over 12 weeks of treatment	53	89
Kaplan-Meier (%)	26	60
Difference in proportions (%) [95% CI]	-25 [-35, -14]	

Modified ITT: ≥ 1 dose of study drug.

There were 67 patients in the Aranesp arm who had their dose increased from 2.25 to 4.5 µg/kg/week, at any time during the treatment period. Of the 67 patients who received a dose increase, 28% had a 20 g/L increase in haemoglobin over baseline, generally occurring between weeks 8 to 13. Of the 89 patients who did not receive a dose increase, 69% had a 20 g/L increase in haemoglobin over baseline, generally occurring between weeks 6 to 13.

In the same study, the effect of Aranesp on tumour progression and survival was evaluated through long-term surveillance of patients. After a median observation period of approximately 1 year, the median time to disease progression in the Aranesp group ($n = 155$) was 29 weeks (95% CI: 22, 33) compared with 22 weeks (95% CI: 18, 25) in the placebo group ($n = 159$). The median time to death in the Aranesp group was 43 weeks (95% CI: 37, not estimable) compared with 35 weeks (95% CI: 29, 48) in the placebo group.

Clinical studies in cancer patients have demonstrated that darbepoetin alfa has similar effectiveness when administered as a single SC injection either once every three weeks or weekly without any increase in total dose requirements.

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Geriatric use

More than 1,500 Aranesp-treated patients with CRF have been studied; 28% were 65 to 74 years of age and 15% were 75 years or older. Of the 781 cancer patients in clinical studies receiving Aranesp and concomitant chemotherapy, 31% were 65 to 74 years of age, while 12% were 75 and over. No differences in dose requirements, safety or efficacy were observed between geriatric and younger adult patients.

5.2 Pharmacokinetic properties

General

The concentration of Aranesp in the circulation remains above the minimum stimulatory concentration for erythropoiesis for longer than an equivalent molar dose of r-HuEPO. This allows Aranesp to be administered less frequently to achieve the same biological response. The pharmacokinetic properties of Aranesp have been studied in healthy adult subjects, in adult and paediatric CRF patients, and in adult cancer patients. In all cases Aranesp exhibits dose-linearity over the therapeutic dose range.

Absorption

Following SC administration in adult CRF patients, the absorption is slow and rate-limiting. The peak concentration occurs at 34 hours (range: 24 to 72 hours) post-SC administration in adult CRF patients, and bioavailability is approximately 37% (range: 30 to 50%). After SC administration of 2.25 µg/kg to adult cancer patients, Aranesp reached peak concentration at a median of 94.5 hours (range: 70.8 to 123 hours).

Distribution

Distribution following IV administration of Aranesp in adult CRF patients is predominantly confined to the vascular space (approximately 60 mL/kg). The distribution half-life following IV administration is 1.4 hours.

Excretion

In adult CRF patients, the terminal half-life of Aranesp following IV administration is approximately 21 hours (range: 12 to 40 hours). Following monthly SC administration in CRF patients and once every 3-week SC dosing in cancer patients, the terminal half-life was 70 hours (range: 35 to 139 hours) in CRF patients and 74 hours (range: 24 to 144 hours) in cancer patients, respectively, reflecting the long absorption half-life.

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Multiple dosing

With once weekly dosing in adult CRF patients, steady-state serum concentrations are achieved within 4 weeks with < 2-fold increase in peak concentration. Accumulation was negligible following both SC and IV dosing over 1 year of treatment.

In adult cancer patients, the pharmacokinetic properties did not change with multiple dosing over 12 weeks (dosing every week or every 2 weeks). The expected moderate increases (less than 2-fold) in Aranesp serum concentrations upon multiple dosing were observed as steady state was approached. No unexpected accumulation was observed upon repeated administration of Aranesp across a wide range of doses at once weekly and once every 2-week dosing schedules.

Special populations

Paediatric

The pharmacokinetic parameters of Aranesp in paediatric CRF patients are similar to adult CRF patients. Following SC or IV administration in children 7 to 16 years old, the terminal half-life was 21 hours (range: 12 to 25 hours) for IV administration and 33 hours (range: 16 to 44 hours) for SC administration. The SC bioavailability was 52% (range: 32 to 70%).

Hepatic dysfunction

The efficacy and safety of Aranesp have not been established in patients with hepatic dysfunction.

5.3 Preclinical safety data

Genotoxicity

Darbepoetin alfa was not mutagenic in assays for gene mutations (bacterial and CHO cell) and was not clastogenic in the mouse micronucleus assay.

Carcinogenicity

Darbepoetin alfa has not been evaluated in standard carcinogenicity bioassays, but there was no evidence from preclinical studies of a proliferative response of any tissue type, other than erythroid progenitor cells, to the drug.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aranesp is formulated at pH 6.2 with 0.05 mg polysorbate 80, 2.12 mg monobasic sodium phosphate monohydrate, 0.66 mg dibasic sodium phosphate and 8.18 mg sodium chloride in Water for Injection (to 1.0 mL).

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store at 2°C to 8°C (Refrigerate. Do not freeze). Protect from light. Do not shake.

Aranesp kept within the pre-filled syringe does not show any observable decrease or change in activity and protein integrity if stored outside the recommended temperature range (not below -20°C or above 30°C) for up to 2 days.

The function of the pre-filled pen when stored beyond the recommended storage condition is not known.

6.5 Nature and contents of container

Aranesp is provided in a glass syringe with a stainless steel 27-gauge needle and is available in the following presentations and packages:

Pre-filled pen:

The needle shield for the pre-filled pen contains dry natural rubber (a derivative of latex).

Aranesp pre-filled pens contain a pre-filled syringe within a sealed, single use pre-filled pen assembly and are available in a pack containing 1 pen, in the following doses:

Presentations available in Australia:

20 µg/0.50 mL, 40 µg/0.40 mL, 60 µg/0.30 mL, 80 µg/0.40 mL, 100 µg/0.50 mL, 150 µg/0.30 mL.

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Presentations not available in Australia:

10 µg/0.40 mL, 15 µg/0.38 mL, 30 µg/0.30 mL, 50 µg/0.50 mL, 200 µg/0.40 mL, 300 µg/0.60 mL, 500 µg/1.0 mL.

Pre-filled syringe with automatic needle guard:

The needle cover for the pre-filled syringe with automatic needle guard contains dry natural rubber (a derivative of latex).

Aranesp pre-filled syringes with automatic needle guard consist of the pre-filled syringe preassembled inside a single use, disposable, automatic needle guard and are available in a pack containing 4 syringes, in the following doses:

Presentations available in Australia:

20 µg/0.50 mL, 30 µg/0.30 mL, 40 µg/0.40 mL, 50 µg/0.50 mL, 60 µg/0.30 mL, 80 µg/0.40 mL, 100 µg/0.50 mL, 150 µg/0.30 mL.

Presentations not available in Australia:

15 µg/0.38 mL, 200 µg/0.40 mL, 300 µg/0.60 mL, 500 µg/1.0 mL.

Pack containing 1 syringe.

Pre-filled syringe:

The needle cover for the pre-filled syringe contains dry natural rubber (a derivative of latex).

Aranesp pre-filled syringes are available in a pack containing 4 syringes, in the following doses:

Presentations available in Australia:

10 µg/0.40 mL

Presentations not available in Australia:

15 µg/0.38 mL, 20 µg/0.50 mL, 30 µg/0.30 mL, 40 µg/0.40 mL, 50 µg/0.50 mL, 60 µg/0.30 mL, 80 µg/0.40 mL, 100 µg/0.50 mL, 150 µg/0.30 mL, 200 µg/0.40 mL, 300 µg/0.60 mL, 500 µg/1.0 mL.

Pack containing 1 syringe.

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6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure

Aranesp (darbepoetin alfa) is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Aranesp stimulates RBC production (erythropoiesis) by the same mechanism as recombinant human erythropoietin (r-HuEPO). Aranesp is a 165-amino acid protein containing 5 N-linked oligosaccharide chains, whereas erythropoietin contains only 3. The additional carbohydrate chains increase the molecular weight of the glycoprotein from approximately 30,000 to 37,000 daltons.

CAS number

209810-58-2

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 Prescription Medicine

8. SPONSOR

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9. DATE OF FIRST APPROVAL

Date of first inclusion in the Australian Register of Therapeutic Goods: 13 JULY 2001

10. DATE OF REVISION

23 August 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Reformatted to new Australia PI template & minor editorial changes
4.2	Additional safety language

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