Drug Monograph

Drug Name | Mechanism of Action and Pharmacokinetics | Indications and Status | Adverse Effects | Dosing | Administration Guidelines | Special Precautions | Interactions | Recommended Clinical Monitoring | Supplementary Public Funding | References | Disclaimer

A - Drug Name

darbepoetin

SYNONYM(S): NESP; novel erythropoiesis stimulating protein

COMMON TRADE NAME(S): Aranesp ® (Amgen)

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B - Mechanism of Action and Pharmacokinetics

Erythropoietin is a glycoprotein produced in the kidney, which stimulates the division and differentiation of committed erythroid progenitors in the bone marrow. Darbepoetin alfa is an analogue of human erythropoietin produced in Chinese Hamster ovary cells by recombinant DNA technology. The final molecule is a recombinant 165 amino acid glycoprotein with additional N- and O-linked oligosaccharide chains as compared to endogenous erythropoietin, but it stimulates erythropoiesis by the same mechanism as the natural one. The high number of sialic acid (bonded by the extra chains) moieties in darbepoetin alfa results in a prolonged half-life and permits a reduction in the frequency of administration. Darbepoetin alfa is used for the non-emergency increase/maintenance of red cell levels, and to decrease the need for transfusions in patients who do not have other reversible anemias such as iron or folate deficiencies, hemolysis or gastrointestinal bleeding. Recently reported clinical trials in a number of tumour types suggest an adverse effect (poorer progression free survival/survival) in patients treated with darbepoetin.

Absorption	Oral: no	
	Bioavailability	SC route: 37% (CRF patients). (Erythropoietin may be degraded in the skin by peptidases.)
Distribution	With Q3 weekly dosing, peak serum concentrations were achieved at a mean time of 71 hours following subcutaneous injection of darbepoetin alfa. Pharmacokinetics were approximately linear to dose and there was no evidence of accumulation.	
	Cross blood brain barrier?	yes

	PPB	unlikely
Metabolism	The metabolic fate of endogenous erythropoietin and the recombinant hormone (i.e. darbepoetin alfa) is poorly understood. Most likely site of degradation is in the bone marrow, following erythropoietin mediated receptor uptake, with other possible sites in liver and kidney. Darbepoetin may be desialylated by the action of tissue and blood sialidases, followed by hepatocyte uptake by galactose receptors. With epoetin alfa, the inactive metabolite appears to undergo hepatic clearance via metabolic pathways and/or binding.	
	Active metabolites	no
	Inactive metabolites	Desialylated metabolite
Elimination	Half-life	(terminal) : 74 hours
	Urine	(unchanged): unknown

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C - Indications and Status

Health Canada Approvals:

- Treatment of Anemia in Cancer Patients with advanced or metastatic, non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy (See Health Canada Advisories: Important Safety Information and New Prescribing Information for the Erythropoiesis-Stimulating Agents, Aranesp® (darbepoetin alfa) and Eprex® (erythropoietin alfa)) **The risk-benefit must be carefully considered and discussed with each patient, especially in patients where red cell transfusions are preferred such as those with a reasonably long life expectancy . Not indicated for the treatment of anemia in patients receiving non-cytotoxic chemotherapy.**
- Treatment of Anemia of Chronic Kidney Disease (CKD) (see product monograph for details).

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D - Adverse Effects

Emetogenic potential: Not applicable

Extravasation Potential: Not applicable

The following table contains adverse effects reported in cancer patients receiving chemotherapy.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**		
Cardiovascular	Arterial/venous thromboembolism (6%)		E	
	Hypertension (4%)	I	E	
	Hypotension (<1%)	I	E	
Dermatological	Dry skin (<1%)		E	
	Erythema (<1%)		E	
	Hyperhidrosis (<1%)		E	
	Pruritus (<1%)		E	
	Rash (7%)		E	
	Skin ulceration (<1%)		E	
Gastrointestinal	Abdominal pain (<1%)		E	
	Anorexia (<1%)		E	
	Constipation (18%)		E	
	Dehydration (5%)		E	
	Diarrhea (22%)		E	
	Dry mouth (<1%)		E	
	Dyspepsia (<1%)		E	
	GI hemorrhage (<1%)		E	
	Mucositis (<1%)		E	
	Nausea, vomiting (<1%)		E	
General	Edema (21%)		E	
	Fatigue (33%)		E	
	Fever (19%)		E	
	Pain (chest pain <1%)	I	E	
	Rigors (<1%)		E	
Hematological	Bruising (<1%)		E	
	Pure red cell aplasia (very rare)			L
	Thrombocytopenia (<1%)		E	
Hypersensitivity	Allergic reaction (<1%)	I		
	Anaphylaxis	I		
	Angioedema	I		
Infection	Sepsis (<1%)		E	
Injection site	Hematoma (<1%)		E	
	Injection site reaction (4%) (pain)	I		
Metabolic / Endocrine	↓ Mg (<1%)		E	
Musculoskeletal	Arthralgia (13%)	I	E	
	Muscle weakness (<1%)	I	E	

	Myalgia (8%)	I	E
Nervous System	Dizziness (14%)		E
	Dysgeusia (<1%)		E
	Headache (12%)	I	E
	Insomnia (<1%)		E
	Paresthesia (<1%)		E
	Peripheral neuropathy (<1%)		E
	Seizure (<1%)		E
Ophthalmic	Eye disorders (abnormal vision; <1%)		E
	Watering eyes (<1%)		E
Respiratory	Cough (<1%)		E
	Dyspnea (<1%)		E
	Pharyngitis (<1%)		E
Urinary	Nocturia (<1%)		E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.
Dose-limiting side effects are underlined.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most frequently reported adverse effects with darbepoetin alfa were ***fatigue, edema and diarrhea***.

The most ***serious adverse effects*** associated with darbepoetin alfa are ***hypertension, seizure*** *and* ***thrombotic events. Use in clinical trials is associated with poorer survival.*** Incidences of most of the other adverse effects in clinical trials are similar in the darbepoetin and in the placebo groups.

Increase in blood pressure associated with darbepoetin alfa is dose-dependent. It can aggravate existing ***hypertension*** especially with a rapid increase in hemoglobin, and is most commonly seen in patients with chronic renal failure. Antihypertensive therapy may be required in up to 40% of patients. Patients with uncontrolled hypertension should not be treated with darbepoetin alfa. If blood pressure cannot be controlled, darbepoetin alfa should be discontinued until blood pressure control is re-established.

Thrombotic/vascular events, such as cerebrovascular accidents, thrombosis (including deep venous thrombosis), cerebral arterial occlusion, and pulmonary emboli have been reported in patients receiving darbepoetin alfa. Patients with pre-existing vascular disease and/or at risk for thrombosis should be monitored closely. Erythropoietic therapies may increase the risk of thrombotic vascular events, which can be fatal. This increased risk of thrombotic events may be associated with treatment to higher hemoglobin concentrations, and/or higher rates of rise of

hemoglobin. The hemoglobin level should be managed carefully, with a target not to exceed 120 g/L in men or women, and the rate of rise of hemoglobin should not increase by more than 10 g/L in any 2-week period or 15g/L in any 3-week period.

There is a ***higher risk of death and serious cardiovascular*** adverse events when patients are treated to target hemoglobin levels of greater than 120 g/L, and when cancer patients not being treated with either radiation or chemotherapy are treated to target hemoglobin levels of 120 g/L. Also refer to **CCO Practice Guidelines**: Treatment of Anemia with Erythropoietic Agents in Patients with Cancer.

In post-marketing reports, ***pure red cell aplasia*** (PRCA) has been reported very rarely in chronic renal failure patients. Anaphylactic reactions and serious allergic reactions have been reported; symptoms can recur with re-challenge.

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E - Dosing

Refer to protocol by which patient is being treated. Red cell transfusion is the preferred method of managing anemia in cancer patients. Darbepoetin should only be used where red cell transfusions are not appropriate in patients and only for patients receiving cytotoxic therapy.

Other causes of anemia should be excluded before instituting therapy with darbepoetin alfa. Iron status should be evaluated for all patients prior to and during treatment and iron supplementation should be administered if necessary. Transferrin saturation should be at least 20%, and serum ferritin levels should be at least 100 ng/mL. Supplemental iron, e.g. oral elemental iron or intravenous iron is recommended to increase and maintain transferrin saturation to levels that will adequately support darbepoetin alfa-stimulated erythropoiesis.

The dose of ESA must be titrated to gradually increase the hemoglobin concentration (not more than 10 g/L in any 2-week period or 15g/L in any 3-week period) to the lowest level sufficient to avoid blood transfusions. **Hemoglobin levels during ESA treatment should not exceed 120 g/L**. Blood pressure should be adequately controlled prior to initiation of darbepoetin alfa therapy, and must be closely monitored and controlled during treatment.

Adults:

Chemotherapy induced anemia in patients with non-myeloid malignancies:

Do not initiate if hemoglobin levels ≥ 100 g/L. Discontinue following the completion of chemotherapy or if no response (no ↓ in RBC transfusion or ↑ in hemoglobin) after 8 weeks of therapy.

Starting dose: 500 µg SC Q3 weekly or

2.25 µg/kg SC once weekly

Dose titration:

Q3 weekly dosing:

- The dose should be adjusted to achieve and maintain a hemoglobin level sufficient to avoid blood transfusions (<120 g/L). Hemoglobin levels should be monitored, prior to dosing, then every 3 weeks thereafter.

Observation	Action
• No response after 8 weeks	**Discontinue**
• Hemoglobin reaches level needed to avoid RBC transfusion OR • Hemoglobin ↑ > 10 g/L in a 2 week period OR • Hemoglobin ↑ > 15 g/L in a 3 week period	**Reduce** dose by 40%#
• Hemoglobin exceeds 120 g/L or level needed to avoid blood transfusion)	**Hold** until hemoglobin approaches level where RBC transfusion may be needed, and then restart with a 40%# dose reduction from previous dose

from Aranesp® product monograph. The Hematology Disease Site Group recommends a 50% dose reduction when the hemoglobin rises >10 g/L in any 2-week period or when the hemoglobin concentration > 120 g/L. Refer to **CCO Practice Guidelines**: Treatment of Anemia with Erythropoietic Agents in Patients with Cancer.

Once weekly dosing:

- Hemoglobin levels should be monitored, prior to dosing, on a weekly basis until hemoglobin level sufficient to avoid blood transfusions (<120 g/L) is reached, and then every 3 weeks thereafter.

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Once weekly dosing:

Observation	Action
After 6 weeks • Hemoglobin has not increased by > 10g/L OR • Unsatisfactory reduction of RBC transfusion required	**May** ↑ to 4.5 µg/kg/week. If no response after 4 weeks, response unlikely → discontinue treatment
• Hemoglobin reaches level needed to avoid RBC transfusion OR • Hemoglobin ↑ > 10g/L in a 2 week period or ↑ > 15g/L in a 3 week period	**Reduce** dose by 40%#
• Hemoglobin > 120 g/L or level needed to avoid RBC transfusion	**Hold** until hemoglobin approaches level where RBC transfusion may be needed, and then restart with a 40%# dose reduction from previous dose

from Aranesp® product monograph. The Hematology Disease Site Group recommends a 50% dose reduction when the hemoglobin rises >10 g/L in any 2-week period or when the hemoglobin concentration > 120 g/L. Refer to **CCO Practice Guidelines**: Treatment of Anemia with Erythropoietic Agents in Patients with Cancer.

Dosage with Toxicity:

General dose modifications for toxicities:

Toxicity	Action
Anaphylaxis or severe allergic reaction	**Discontinue**
Antibody-mediated anemia (i.e. PRCA)	**Discontinue**; DO NOT switch to other erythropoietic agents as cross-reactivity may occur
Blood pressure not controlled by pharmacologic or dietary restrictions	Discontinue, until blood pressure controlled

Dosage with Hepatic Impairment:

No information found. The safety and efficacy of darbepoetin alfa have not been studied in patients with hepatic impairment.

Dosage with Renal Impairment:

Based on information to date, the use of darbepoetin alfa in predialysis patients does not accelerate the rate of progression of renal insuffiiciency.

Dosage in the elderly:

No difference in safety and efficacy in elderly patients as compared to younger patients

Children:

Safety and efficacy have not been established.

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F - Administration Guidelines

- Refrigerate (2-8°C) but do not freeze. Protect from exposure to light. Do not shake.
- Subcutaneous self-administration (or administered by home caregiver); drug available by outpatient prescription.
- Do not administer by intravenous infusion or mix with other drugs
- Available as single-dose vial of 15, 25, 40, 60, 100, 200, 325, or 500 µg darbepoetin alfa per vial, containing polysorbate 80 as stabilizer.
- Available as pre-filled syringe of 10, 15, 20, 30, 40, 50, 60, 80, 100, 130, 150, 200, 250, 300, 400 or 500 µg darbepoetin alfa, containing polysorbate 80 as stabilizer.

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G - Special Precautions

Other:

Darbepoetin alfa is **contraindicated** for prophylactic use in surgical patients, in patients who developed pure red cell aplasia (PRCA) following treatment with any erythropoiesis regulating hormone, with uncontrolled hypertension, and with known hypersensitivity to mammalian cell-derived products or any component in darbepoetin alfa preparation. It is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless also receiving concomitant myelosuppressive chemotherapy.

Use with caution in patients with risk factors or thrombosis, pre-existing cardiovascular disease and patients unlikely to be able to tolerate anticoagulant therapy.

Recent clinical trials suggest a possible tumour promoter effect. Darbepoetin is non-mutagenic, non-genotoxic and not clastogenic. Although animal studies did not demonstrate placental transfer or fertility changes, darbepoetin may have **fetotoxic** effects. It is not known whether darbepoetin alfa can affect reproduction capacity or cause fetal harm when administered to pregnant women; therefore, it should be given to a **pregnant** woman only if potential benefit justifies the potential risk to the fetus. The possibility of potential pregnancy should be discussed and the need for contraception evaluated. It is not known whether darbepoetin alfa is excreted in human milk; thus **breast feeding** is not recommended.

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H - Interactions

No evidence exists that indicates treatment with darbepoetin alfa alters the metabolism of other drugs.

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

- Neutralizing antibodies if sudden loss of response occurs
- Serum vitamin B12 and folate; baseline
- Iron evaluation (includes transferrin saturation and serum ferritin); baseline and regular
- Hematocrit/ hemoglobin levels; once weekly (once weekly dosing) or every 3 wks (q3w dosing) until stabilized, then q3w thereafter (discontinue when hemoglobin ≥ 120g/litre)
- Blood pressure monitoring; baseline and regular
- Clinical assessment for thomboembolism; regular
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- Anemia secondary to MDS, with specific criteria

ODB Limited Use (ODB Formulary)

- Patients with cancer diagnosis and receiving chemotherapy, with specific criteria

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K - References

Amgen press release Nov 30th, 2007. Amgen announces interim results of Aranesp® "PREPARE" study in breast cancer patients. Thousand Oaks, CA, USA.

Asif M, Siddique A, Keating GM. Darbepoetin Alfa. A Review of its Use in the Treatment of Anaemia in Patients with Cancer Receiving Chemotherapy. Drugs 2006; 66 (7): 997-1012

CCO Practice Guidelines: Treatment of Anemia with Erythropoietic Agents in Patients with Cancer

E- American Society of Health-System Pharmacists. July 16th, 2007 (accessed): Darbepoetin alfa.

FDA Drug Warning Letter: Additional Trials Showing Increased Mortality and/or Tumor Progression with Epogen®/Procrit® and Aranesp®. March 7th, 2008 (Amgen and Ortho-Biotech)

Health Canada endorsed important safety information on erythropoiesis-stimulating agents (ESAs): Aranesp® (darbepoetin alfa) and Eprex® (erythropoietin alfa). April 16th, 2007

Jelkmann W. The enigma of the metabolic fate of circulating erythropoietin (Epo) in view of the pharmacokinetics of the recombinant drugs rhEpo and NESP. Eur J Haematol 2002; 69(5-6): 265-74.

Product Monograph: Aranesp® (Darbepoetin). Amgen Canada Inc., January 16, 2009.
Xenocostas A, Cheung WK, Farrell F et al. The pharmacokinetics of erythropoietin in the cerebrospinal fluid after intravenous administration of recombinant human erythropoietin. Eur J Clin Pharmacol 2005; 61(3): 189-95.

March 2013: Added public funding info; revised Feb 2010

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

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Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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