Erythropoietin (EPO)
Newborn use only

2022

Alert	Erythropoiesis stimulating agents (ESAs) are S100 medication used for the prevention/treatment of anaemia associated with intrinsic renal disease. May require additional approval per local hospital policy/procedure for other indications.
Indication	Prevention of anaemia in preterm infants. Prevention and treatment of anaemia in chronic kidney disease (CKD).
Action	Endogenous glycoprotein that stimulates red blood cell production. It is produced by the kidney.
Drug type	Erythropoiesis stimulating agent (ESA)
Trade name	Eprex: Epoetin alfa NeoRecormon: Epoetin beta Aranesp: Darbepoetin alfa
Presentation	Epoetin alfa (Eprex): 1000 unit/0.5 mL* prefilled syringe. Epoetin beta (NeoRecormon): 2000 unit/0.3 mL* Darbepoetin (Aranesp): 10 microgram/0.4 mL* *These are the recommended strengths. Other strengths are available – check carefully.
Dose	**Prevention of Anaemia of Prematurity** **ANMF group does not recommend erythropoietin as a routine treatment for this indication and to be considered only in special circumstances.** **Epoetin therapy requires concomitant elemental iron (ORAL 3-6 mg/kg/day or IV 20 mg/kg/dose weekly).** Refer to Iron formulary for further guidance. **Epoetin alfa:** 400 units/kg/dose 3 times weekly (e.g. Mon/Wed/Fri) commencing from day 3 of life for 6 weeks or more OR up to 35 weeks gestation.[1,2] **Epoetin beta:** 250 units/kg/dose 3 times weekly (e.g. Mon/Wed/Fri) commencing from day 3 of life for 6 weeks or more.[3-4] **Darbepoetin alfa:** 10 microgram/kg once weekly for 6 weeks or more OR up to 35 weeks corrected gestation. **Chronic Kidney Disease (CKD)** **Darbepoetin alfa:** 0.5 microgram/kg once weekly.[16-19] (ANMF consensus).* *Adjust dose to target a haemoglobin of 95-110 g/L.[19] *Adjust iron supplement to target transferrin saturation >20% and serum ferritin >100 microgram/L. *Weekly doses can be accumulated to 2-4 weekly intervals (e.g. 1 microgram/kg every 2 weeks or 2 microgram/kg every 4 weeks). *Neonates, particularly preterm neonates may need higher doses of 1-1.5 microgram/kg once a week.[18,19]
Dose adjustment	Therapeutic hypothermia – Not applicable. ECMO – No information. Renal impairment – No information. Hepatic impairment – No information.
Maximum dose	Epoetin alfa: 1200 unit/kg/week.[5-7] Epoetin beta: 750 unit/kg/week. Darbepoetin: 10 microgram/kg/week.
Total cumulative dose	
Route	SC, IV
Preparation	SC injection: Ready to use. Allow to reach room temperature before use. Do not shake. IV injection Epoetin alfa: Draw up 0.5 mL (1000 units) epoetin alfa and add 4.5 mL sodium chloride 0.9% to make a solution with a final volume of 5 mL and final concentration of 200 unit/mL.[3,4,8,12]

	Epoetin beta: Draw up 0.3 mL (2000 units) epoetin beta and add 9.7 mL sterile water to make a solution with a final volume of 10 mL and final concentration of 200 unit/mL.[3,4] Darbepoetin alfa: Anaemia of prematurity: Draw up 0.4 mL (10 microgram) darbepoetin alfa and add 0.6 mL sodium chloride 0.9% to make a solution with a final volume of 1 mL and final concentration of 10 microgram/mL. Note: For infants>1 kg, multiple syringes of 10 microgram/mL solution may be required. CKD: Draw up 0.4 mL (10 microgram) darbepoetin alfa and add 9.6 mL sodium chloride 0.9% to make a solution with a final volume of 10 mL and final concentration of 1 microgram/mL.
Administration	SC injection (preferred). IV injection over 1-5 minutes using the proximal IV bung.
Monitoring	Continuous cardio-respiratory monitoring, blood pressure (before and during therapy). Full blood count and reticulocyte count weekly.
Contraindications	Known sensitivity to mammalian cell derived products. Hypersensitivity to the active substance or to any of the excipients. Pure red cell aplasia following erythropoietin therapy. Uncontrolled hypertension.
Precautions	Anaphylactic reactions have been reported. Give the first dose under medical supervision. Resuscitation facilities must be readily available. Use with caution in patients with history of seizures or medical conditions associated with a predisposition to seizure activity.
Drug interactions	There are no known clinically significant drug interactions but the effect of Eprex may be potentiated by the simultaneous therapeutic administration of a haematinic agent such as ferrous sulphate when a deficiency state exists. Drugs that decrease erythropoiesis may decrease the response to Eprex.
Adverse reactions	Hypertension, seizures. Neutropenia and thrombocytosis. Transient erythema at site of subcutaneous injection. Diarrhoea, vomiting, pyrexia. Hypersensitivity including rash, urticaria and angioneurotic oedema may occur.
Compatibility	Do not dilute or mix with other drugs.
Incompatibility	Eprex: Midazolam, vancomycin
Stability	Eprex is stable for 7 days below 25°C.[20] NeoRecormon is stable for 3 days below 25°C.[20] Aranesp prefilled syringes (only) are stable at room temperature up to 30°C for 2 days. May be used if inadvertently frozen for less than 2 days.[20]
Storage	Store at 2–8°C. Do not freeze or shake. Protect from light.
Excipients	Aranesp: Polysorbate-80, sodium chloride, dibasic sodium phosphate dihydrate and monobasic sodium phosphate dihydrate. Eprex: Glycine, polysorbate-80, sodium chloride, dibasic sodium phosphate dihydrate, monobasic sodium phosphate dihydrate and sodium citrate. NeoRecormon: Urea, sodium chloride, monobasic sodium phosphate, dibasic sodium phosphate dodecahydrate, calcium chloride dihydrate, polysorbate 20, glycine, leucine, isoleucine, threonine, glutamic acid, phenylalanine.
Special comments	Ensure adequate iron stores and if necessary, start iron supplementation before starting epoetin.
Evidence	**Efficacy** **<u>Anaemia of prematurity</u>** **<u>Early use of erythropoietin (<8 days of age)</u>** Ohlsson et al. 2020 Cochrane review evaluated 34 studies enrolling 3643 infants.[9] While early administration of ESAs reduced the use of red blood cell (RBC) transfusions, there was a moderate

heterogeneity among the included studies and the quality of the evidence was low. The volume of RBCs transfused and donor exposure were also reduced but reductions were small and were likely to be of limited clinical importance. There was no significant difference in the rate of severe ROP or mortality. There was a significant reduction in the incidence of severe IVH, PVL and NEC. Neurodevelopmental outcomes varied in the studies.

Late use of erythropoietin (≥8 days of age)

Aher et al. 2020 Cochrane review evaluated 31 studies and 1651 preterm infants.[10] Most studies in the trial included small sample size. There was moderate heterogeneity and the quality of evidence was very low. There was a significant reduction in the use of one or more transfusions, but no significant reduction in the total volume (mL/kg) of blood transfused per infant. There was a trend in increased of ROP. There were no significant differences in other clinical outcomes including mortality and necrotising enterocolitis. Long-term neurodevelopmental outcomes were not reported.

Low dose (≤500 IU/kg/week) versus high dose (>500 IU/kg/week)

Subgroup analysis by Ohlsson et al. showed both low and high dose had similar reduction in the use of one or more transfusions. (Low dose: typical RR 0.77, 95% CI 0.65 to 0.91 versus high dose: typical RR 0.79, 95% CI 0.74 to 0.86).[9]

Low iron (≤5 mg/kg/day) versus high iron (>5 mg/kg/day) supplementation during EPO therapy

Subgroup analysis by Ohlsson et al. showed the following: High dose iron supplementation with either low or high dose EPO therapy showed similar reduction in the use of one or more RBC transfusions. Low dose iron supplementation with high dose EPO therapy showed significant reduction, but low dose iron and low dose EPO therapy showed no significant reduction in the use of one or more RBC transfusions.[9]

Dosing regimens: Trials by Maier et al. and Ohls et al. added 47% weight to the population size in Ohlsson's meta-analysis. Dosage regimens of these trials were further reviewed for this formulary.

Epoetin alfa: 1995 and 1997 trials by Ohls et al. administered 200 units/kg/day of epoetin alfa given as 4-hour IV infusion mixed in 2 mL of 5% albumin or parenteral nutrition solution.[1, 2] EPO was commenced at less than 48 hours of age and continued for 14 consecutive days. Ohls 2001 et al. tested 400 units/kg 3 times weekly, commencing before 96 hours of age and continued until discharge, transfer, death or 35 weeks corrected gestational age. EPO was administered as 1 hour IV infusion or SC injection.[11]

Epoetin beta: Maier 1994 et al. administered 250 units/kg of epoetin beta 3 times a week subcutaneously from day 3 to day 42.[3] Maier et al. 2002 administered 250 units/kg of epoetin beta 3 times a week as either IV bolus or SC until days 65-68 of life.[4]

Darbepoetin alfa: The conversion ratio of darbepoetin and erythropoietin is 1 microgram of darbepoetin = 240 IU of epoetin.[17] Roohi et al. evaluated reticulocyte responses to SC darbepoetin in preterm infants in a blinded dose-response study. Preterm infants respond by increasing erythropoiesis in a dose-dependent fashion, with the greatest reticulocyte response occurring with 10 microgram/kg/dose.[14] Ohls et al. conducted an RCT in preterm infants 500 g to 1250 g birth weight and <48 hours of age and were randomised to darbepoetin alfa (10 microgram/kg once weekly subcutaneously), EPO (400 U/kg 3 times per week subcutaneously) or placebo through 35 weeks' gestation. Infants receiving darbepoetin or EPO received fewer transfusions and fewer donor exposures and fewer injections were given to darbepoetin recipients.[15]

The proposed range in the formulary is a pragmatic modified regimen from these trials.

Chronic kidney disease (CKD)

Kidney Disease: Improving Global Outcomes (KDIGO) recommendations in children with CKD is a starting dose of 20-50 IU/kg 3 times weekly of epoetin alfa or beta and a dose of 0.45 microgram/kg once weekly or 0.75 microgram/kg every 2 weeks for darbepoetin. The objective is to increase the haemoglobin level by 10-20 g/L every 4 weeks.[16] The conversion ratio of darbepoetin and erythropoietin is 1 microgram of darbepoetin = 240 IU of EPO.[17] Observational data from the North American Paediatric Renal Transplant Cooperative Study (NAPRTCS) 2004 registry report suggests higher dosage in younger infants, ranging from 275 to 350 U/kg per week.[18] This equates to 1.1-1.5 microgram/kg/week of darbepoetin. In a retrospective cohort study, Durkan et al. reported usage of darbepoetin in 6 infants with CKD weighing less than 8 kg. They were started on 0.5 microgram/kg per week of darbepoetin for 20 weeks. The dose was then titrated by approximately 25% between 0.25 microgram/kg/week to 1.2 microgram/kg/week, given at intervals of 1-4 weeks as per transferrin saturation and ferritin status to maintain haemoglobin (Hb) level

	of 100-110 g/L. (Example, a baby on a dose of 0.5 microgram/kg/week might have been given a dose of 1.5 microgram/kg every 3 weeks). No side effects were reported.[19] **The proposed dose range for CKD in the formulary is a pragmatic consensus modified regimen by the ANMF group in consultation with paediatric nephrologists.** **Fluid compatibility** Stability and adsorption characteristics of epoetin alfa in various commonly used intravenous fluids was tested by Ohls et al.[8] Epoetin alfa was diluted to 0.1 unit/mL for the study. Fluids tested were sterile water, Naci 0.9%, dextrose 10% in water, dextrose 10% with albumin at concentrations of 0.01 %, 0.05%, and 0.1 % and total parenteral nutrition solution containing either 0.5% or 2.25% amino acids. Concentrations declined significantly in all fluids containing less than 0.05% protein, but remained stable over 24 hours in fluids containing 0.05% more protein. Exception was sodium chloride 0.9%. 95.5% of epoetin alfa was recovered following passage through intravenous tubing, T-connector and intravenous cannula and the subsequent recovery percentage over a 24-hour infusion period was 84.7% ± 5%. Widness et al. found that loss of epoetin alfa in low-protein solutions was 25-30% with 10 units/mL and no loss with 100 units/mL.[12] Maier et al. dissolved epoetin beta with sterile water so that injected volume is 0.25 mL to 0.55 mL SC or IV bolus.[3, 4] **Pharmacokinetics** No single route of administration has been found to be more efficacious than another. Pharmacokinetics of EPO were studied in a group of very low birth weight infants after both intravenous and subcutaneous administration.[13] After the IV doses, serum erythropoietin concentrations showed a uniform decline with a half-life of 8.1 ± 2.7 hours. After the SC doses, peak concentrations occurred at 2 to 11.9 hours, and elevated concentrations were maintained for 24 hours. In contrast to IV EPO, the pharmacokinetics of SC EPO were variable, most likely as a result of erratic absorption from subcutaneous sites in preterm infants because the volume of distribution and clearance in the same infants after the intravenous doses were more uniform. The variable absorption from one infant to another may make dose adjustments necessary during long-term treatment and will depend on individual haematocrit response.[13] **Safety** Major RCTs do not demonstrate any significant differences in short term side effects between treatment and control groups.[1-4]
Practice points	Routine use of EPO to reduce the amount of blood transfusion in preterm or low birthweight infants is not currently recommended because of limited clinical benefits.[9] The pragmatic dosing recommendation in this formulary is based on 4 major trials.[1-4] Both low (≤5 mg/kg/day) and high (>5 mg/kg/day) dose iron supplementation show similar reduction in the number of one or more transfusions with high dose EPO dosing schedule chosen in this formulary.[9]
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