Erythropoietin (EPO) - Human Recombinant 2021

Newborn use only

Alert	S100 medication – may require additional approval per local hospital policy/procedure.
Indication	To decrease the need for RBC transfusions in extremely low birth weight infants Replacement of low endogenous erythropoietin Support to maintain/ accelerate erythropoiesis Augmenting haemoglobin level
Action	Endogenous glycoprotein that stimulates red blood cell production. It is produced by the kidney.
Drug type	Erythropoietin agonist.
Trade name	Eprex (EPOETIN ALFA)
Presentation	1000 unit/0.5mL prefilled syringe (recommended). Other strengths are available – check carefully.
Dose	250-400 unit/kg/dose 3 times weekly (e.g. Mon/Wed/Fri) for commencing from day 3 of life and up to 35 weeks corrected age.(1-4) Requires concomitant iron therapy (3-6 mg/kg/day). Refer to Iron formulary for further guidance.
Dose adjustment	Therapeutic hypothermia – Not applicable. ECMO – No information. Renal impairment – No information. Hepatic impairment – No information.
Maximum dose	1200 unit/kg/week (5-7)
Total cumulative dose	
Route	SC, IV
Preparation	SC injection – Ready to use. Alow to reach room temperature before use. Do not shake. IV injection - 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)
Administration	SC injection preferred. IV injection over 1-2 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.
Storage	Store at 2–8 °C. Do not freeze or shake. Protect from light.
Excipients	Glycine, polysorbate-80, sodium chloride, dibasic sodium phosphate dihydrate, monobasic sodium phosphate dihydrate and sodium citrate.
Special comments	Ensure adequate iron stores and if necessary start iron supplementation before starting epoetin.

Evidence	**Efficacy** **Early use of erythropoietin (<8 days of age) in preterm or low birthweight infants** 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) in preterm or low birthweight infants** 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 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. 1995 and 1997 trials by Ohls et al administered 200 units/kg/day 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) Maier 1994 et al administered 250 units/kg of epoetin beta 3 times a week subcutaneously from day 3 to day 42.(3) Lyophilised epoetin beta containing 1000 units in the vial was dissolved with sterile water so that injected volume was 0.25 – 0.55 mL. Maier et al 2002 administered 250 units/kg of epoetin beta 3 times a week as either IV bolus or SC. Epoetin 1000 units in the vial was dissolved with sterile water so that injected volume was 0.25 mL to 0.55 mL.(4) The proposed range in the formulary is a pragmatic modified regimen from these trials. **Fluid compatibility:** Stability and adsorption characteristics of epoetin alfa in various commonly used intravenous fluids was tested by Ohls et al.(8) Epoetin was diluted to 0.1 unit/mL for the study. Fluids tested were sterile water, NaCl 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 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 in low-protein solutions was 25-30% with 10 units/mL and no loss with 100 units/mL.(12) Maier et al dissolved epoetin 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 I 1.9 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 ion supplementation show similar reduction in the number of one or more transfusions with high dose EPO dosing schedule chosen in this formulary.(9)
References	1. Ohls RK, Harcum J, Schibler KR, Christensen RD. The effect of erythropoietin on the transfusion requirements of preterm infants weighing 750 grams or less: a randomized, double-blind, placebo-controlled study. Journal of Pediatrics. 1997;131(5):661-5. 2. Ohls RK, Osborne KA, Christensen RD. Efficacy and cost analysis of treating very low birth weight infants with erythropoietin during their first two weeks of life: a randomized, placebo-controlled trial. Journal of Pediatrics. 1995;126(3):421-6. 3. Maier RF, Obladen M, Scigalla P, Linderkamp O, Duc G, Hieronimi G, et al. The effect of epoetin beta (recombinant human erythropoietin) on the need for transfusion in very-low-birth-weight infants. European Multicentre Erythropoietin Study Group. New England Journal of Medicine. 1994;330(17):1173-8. 4. Maier RF, Obladen M, Muller-Hansen I, Kattner E, Merz U, Arlettaz R, et al. Early treatment with erythropoietin beta ameliorates anemia and reduces transfusion requirements in infants with birth weights below 1000 g. Journal of Pediatrics. 2002;141(1):8-15. 5. Avent M, Cory B, Galpin J, Ballot D, Cooper P, Sherman G, et al. A comparison of high versus low dose recombinant human erythropoietin versus blood transfusion in the management of anaemia of prematurity in a developing country. Journal of tropical pediatrics. 2002;48(4):227-33. 6. Carnielli V, Montini G, Da Riol R, Dall'Amico R, Cantarutti F. Effect of high doses of human recombinant erythropoietin on the need for blood transfusions in preterm infants. The Journal of pediatrics. 1992;121(1):98-102. 7. Carnielli VP, Da Riol R, Montini G. Iron supplementation enhances response to high doses of recombinant human erythropoietin in preterm infants. Archives of Disease in Childhood-Fetal and Neonatal Edition. 1998;79(1):F44-F8. 8. Ohls RK, Christensen RD. Stability of human recombinant epoetin alfa in commonly used neonatal intravenous solutions. Annals of Pharmacotherapy. 1996;30(5):466-8. 9. Ohlsson A, Aher SM. Early erythropoiesis-stimulating agents in preterm or low birth weight infants. Cochrane Database of Systematic Reviews. 2020(2). 10. Aher SM, Ohlsson A. Late erythropoiesis-stimulating agents to prevent red blood cell transfusion in preterm or low birth weight infants. Cochrane Database of Systematic Reviews. 2020(1). 11. Ohls RK, Ehrenkranz RA, Wright LL, Lemons JA, Korones SB, Stoll BJ, et al. Effects of early erythropoietin therapy on the transfusion requirements of preterm infants below 1250 grams birth weight: a multicenter, randomized, controlled trial. Pediatrics. 2001;108(4):934-42. 12. Widness JA, Schmidt RL. Comment: epoetin alfa loss with NaCl 0.9% dilution. Annals of Pharmacotherapy. 1996;30(12):1501-2. 13. Brown MS, Jones MA, Ohls RK, Christensen RD. Single-dose pharmacokinetics of recombinant human erythropoietin in preterm infants after intravenous and subcutaneous administration. The Journal of pediatrics. 1993;122(4):655-7.

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