



		EMLc	ATC codes: V03AC01
Indication	Harmful effects of drugs, medicaments or biological substances, not elsewhere classified ICD11 code: <a href="#">NE60</a>		
INN	Deferoxamine		
Medicine type	Chemical agent		
List type	Complementary (EML) (EMLc)		
Formulations	Parenteral > General injections > unspecified: 500 mg in vial powder for injection (mesilate)		
EML status history	First added in 1979 ( <a href="#">TRS 641</a> ) Changed in 2007 ( <a href="#">TRS 950</a> ) Changed in 2011 ( <a href="#">TRS 965</a> )		
Sex	All		
Age	Also recommended for children		
Therapeutic alternatives	The recommendation is for this specific medicine		
Patent information	Patents have expired in most jurisdictions Read more <a href="#">about patents</a> . 		
Wikipedia	<a href="#">Deferoxamine</a> 		
DrugBank	<a href="#">Deferoxamine</a> 		

## Summary of evidence and Expert Committee recommendations

In 2009, the Expert Committee requested a review of iron chelators for children. The current EMLc includes deferoxamine only, for parenteral use. The Committee noted a recent review of iron chelators (1). Acute iron intoxication can occur in both adults and children and can be fatal. Treatment includes supportive care, and parenteral deferoxamine. Chronic iron overload is due mainly to repeat transfusions, in patients with haemoglobinopathies. Other conditions requiring repeat transfusions include myelodysplastic syndromes, and (more rarely) haemochromatosis. Long-term consequences of chronic iron overload include multiple organ dysfunction (heart, liver, and endocrine), and/or failure, and death. Heart failure due to iron cardiomyopathy is the main cause of death in thalassaemia patients. The Committee reviewed the evidence available for acute iron poisoning. Two studies in volunteers showed that iron removal was possible with high doses of oral deferoxamine. The Committee noted that a recent placebo-controlled trial of deferasirox (20 mg/kg) showed iron elimination after a 5 mg/kg iron dose in volunteers (2). A systematic review of observational and prospective studies suggests beneficial effects of deferoxamine on morbidity (notably cardiac disease and liver iron overload) and mortality, including with subcutaneous use (3-8). In sickle cell disease, evidence is more limited but supports the use of deferoxamine. Deferoxamine has adverse effects on growth and maturation, auditory, and ophthalmic function. The Committee considered that the main limitation of deferoxamine was however the need for prolonged parenteral administration, and a trial showed less compliance with parenteral deferoxamine than oral deferiprone (9). The Committee noted that the evidence supporting use of deferiprone comprises small trials – mostly observational including both adults and children summarized in a Cochrane Review from 2007 (10 trials including 398 participants). The dose used in trials was generally 75 mg/kg per day, and reported adverse effects included neutropenia and agranulocytosis, which require weekly monitoring of blood cell counts. Gastrointestinal symptoms are common and knee arthralgias are reversible. Neurological signs at doses above 100 mg/kg have been reported in children. The use of the combination of deferiprone and deferoxamine was found to be more effective than single agents with promising results of normalization of ferritinaemia (10). The review concluded that there was no consistent

effect on reduction of iron overload among various treatments. Deferoxamine was more effective on iron excretion in three of four trials. Trials did not report on mortality or end organ damage (38). The Committee concluded that the evidence supporting the effectiveness of deferiprone was insufficient. The evidence of effectiveness of deferasirox is more recent and of better quality than is the case for deferiprone. The Committee noted a large nonrandomized uncontrolled prospective company-sponsored trial in 192 patients (64 aged less than 16 years), which showed a statistically significant decrease in cardiac iron (assessed by MRI) after one year of treatment (11). A Cochrane Review of deferasirox in sickle-cell disease identified only one study and concluded that deferasirox appeared to be as effective as deferoxamine, but important outcomes were missing. No data are available to support the current use of deferasirox in myelodysplastic syndromes. The Committee noted that deferasirox has renal adverse effects, which require regular monitoring of renal function. Dose-dependent increases in serum creatinine, which may occur in up to 36% of patients, may not always be reversible. Tubulopathy has also been reported in children with thalassaemia (EU product information). The Committee considered the costs of deferoxamine, including laboratory monitoring cost, adverse effects and/or worsening of underlying disease as a result of non-compliance, hospitalization, parenteral injections, need for carer, and missed school days. The cost of deferasirox treatment may be 2–3 times more than that of deferoxamine, and the cost of deferiprone could be twice that of deferoxamine. The Committee noted that several reports suggest that deferasirox therapy is more cost effective than traditional deferoxamine therapy but considered that a truly unbiased cost comparison between deferiprone and deferasirox has not been published. The Committee noted that reports of costs analysis highlight variation in acquisition costs and resources used (12). The acquisition cost of deferasirox is an important barrier to access, but adherence to infused deferoxamine is also problematic and administration costs also need to be considered. Although noting the advantages of the oral route, the Committee did not recommend the inclusion of deferasirox in the EML and EMLc at this stage, but recommended adding an asterisk to deferoxamine, noting the alternative oral form (deferasirox 500 mg dispersible oral solid dosage form) is available. As an antidote, deferoxamine should be listed on the Complementary List due to the level of care required for its safe use. References: 1. Brittenham GM. Iron chelating therapy for transfusional iron overload. *The New England Journal of Medicine*, 2011, 364:146–156. 2. Griffith EA et al. Effect of deferasirox on iron absorption in a randomized, placebo-controlled, crossover study in a human model of acute supratherapeutic iron ingestion. *Annals of Emergency Medicine*, 2011, 58(1):69–73. 3. Olivieri NF et al. Survival in medically treated patients with homozygous B-thalassemia. *The New England Journal of Medicine*, 1994, 331:574–578. 4. Zurlo MG et al. Survival and causes of death in thalassaemia major. *The Lancet*, 1989, 2:27–30. 5. Borgna-Pignatti C et al. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. *Haematologica*, 2004, 89:1187–1193. 6. Wolfe L et al. Prevention of cardiac disease by subcutaneous deferoxamine in patients with thalassemia major. *The New England Journal of Medicine*, 1985, 312:1600–1603. 7. Brittenham GM et al. Efficacy of deferoxamine in preventing complications of iron overload in patients with thalassemia major. *The New England Journal of Medicine*, 1994, 331:567–573. 8. Roberts D et al. Oral deferiprone for iron chelation in people with thalassemia. *Cochrane Database of Systematic Reviews*, 2007, (3):CD004839. 9. Roberts D et al. Desferrioxamine mesylate for managing transfusional iron overload in people with transfusion-dependent thalassaemia. *Cochrane Database of Systematic Reviews*, 2005, (4):CD004450. 10. Kontoghiorghes GJ. The 18th ICOC proceedings in Athens, Greece: new breakthrough in thalassemia leading to the complete treatment of iron overload and to hundreds of patients achieving and maintaining normal body iron stores. Ethical questions on chelation therapy. *Hemoglobin*, 2010, 34(3):199–203. 11. Tanner MA et al. A randomized, placebo-controlled, double-blind trial of the effect of combined therapy with deferoxamine and deferiprone on myocardial iron in thalassemia major using cardiovascular magnetic resonance. *Circulation*, 2007, 115:1876–1884. 12. Delea TE et al. Cost effectiveness of once-daily oral chelation therapy with deferasirox versus infusional deferoxamine in transfusion-dependent thalassaemia patients: US healthcare system perspective. *Pharmacoeconomics*, 2007, 25:329–342.

