Penicillamine

Essential medicine status

Section: 4. Antidotes and other substances used in poisonings > 4.2. Antidotes and other substances used in poisonings > Specific

ATC codes: M01CC01

Indication	Harmful effects of or exposure to noxious substances, chiefly nonmedicinal as to source, not elsewhere classified ICD11 code: NE61
INN	Penicillamine
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid:** 250 mg
EML status history	First added in 1979 (TRS 641) Changed in 1984 (TRS 722) Changed in 2007 (TRS 950) Changed in 2011 (TRS 965)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Penicillamine
DrugBank	Penicillamine

Summary of evidence and Expert Committee recommendations

Penicillamine as an antidote for heavy metal poisoning in children was deleted from the EMLc following a review in 2011. The Committee acknowledged that lead poisoning is a common and serious poisoning. Most children with lead poisoning are in developing countries, where increased risks (e.g. iron deficiency) and increased exposure to lead are common. While primary prevention of lead poisoning is the most effective, chelation is used to decrease blood levels acutely on the basis of lead levels in blood. In symptomatic patients (encephalopathy), hospitalization is necessary and parenteral chelation is used. The Committee reviewed the evidence available with parenteral and oral chelating medicines. The Committee noted that there are very limited data on penicillamine, a chelator used primarily in Wilson disease. The most commonly used daily dose in the United States is 30 to 40 mg/kg or 600 to 750 mg/m2 body surface area for one to six months. A retrospective study showed that penicillamine is more effective than placebo, decreasing blood lead by about 33%. In a comparative trial, it was as effective as dimercaprol or oral sodium calcium edetate given orally (1) but less effective than parenteral sodium calcium edetate. Penicillamine has major adverse effects (zinc depletion and its consequences, transient leukopenia, thrombocytopaenia, rash, enuresis, and abdominal pain) leading to discontinuation. The Committee noted that adverse effects affected 33% of 84 adult patients treated in a study. Children treated with 15 mg/kg per day may experience fewer adverse effects (2). While penicillamine has been used widely for lead chelation, its safety profile is a concern. The Committee reviewed the evidence available for sodium calcium edetate and dimercaprol and noted that there is considerable experience but limited and low-quality evidence. Two prospective studies showed modest effect on lead excretion, but no benefit on IQ with sodium calcium edetate alone or combined with dimercaprol. The combination increased adverse effects. In contrast, a retrospective comparison of 18 children receiving either dimercaprol or sodium calcium edetate showed no residual intelligence deficit after about three years follow-up, and only a visual deficit more frequent in the dimercaprol group. Dimercaprol is only recommended for use on the first day of treatment of acute poisoning in combination with calcium edetate disodium. The dose is 450 mg/m2 per day and requires 4 to 6 intramuscular (IM) injections due to its short half-life. One case series comparing

sodium calcium edetate (IV, IM) and penicillamine in children, concluded that sodium calcium edetate was more effective on lead excretion than oral penicillamine and should be preferred in severe intoxications (>80 micrograms/dl) (3). The Committee considered safety data available for calcium edetate disodium. In a retrospective series, the most common adverse effect was renal toxicity. The Committee also noted reports of 3 deaths (2 in children) from hypocalcaemia-induced cardiac arrest, in the United States between 2003 and 2005, probably due to confusion with disodium edetate, normally indicated for the emergency treatment of hypercalcaemia. The Committee concluded that, despite the low level of evidence to support its use, sodium calcium edetate had shown effectiveness for lead chelation in children. The Committee considered cost–effectiveness data on different strategies of diagnostic and treatment by either sodium calcium edetate or penicillamine. Sodium calcium edetate dominated penicillamine in the incremental cost–effectiveness ratios (cost per quality-adjusted life year, QALY, and cost per case prevented), unless direct costs for inpatient treatment with sodium calcium edetate were included. The authors also concluded that, based on 200 000 children in the United States with blood lead levels >25 micrograms/dl, chelation therapy could prevent more than 45 000 cases of reading disability per year, resulting in savings of US$ 900 million in overall costs (4). No price data were available to the Committee from the International Price Indicator Guide as the medicines reviewed are not listed there. The Committee recommended that penicillamine be deleted from the EMLc, because of the higher risk of adverse effects in children. The Committee further recommended that the retention of penicillamine on the EML for adults be reviewed. Until this review is completed and considered, penicillamine will remain on the List. References: 1. Bartsocas CS et al: Oral d-penicillamine and intramuscular BAL + EDTA in the treatment of lead accumulation. Acta paediatrica Scandinavica, 1971, 60:553–558. 2. Shannon MW, Townsend MK. Adverse effects of reduced d-penicillamine in children with mild to moderate lead poisoning. The Annals of Pharmacotherapy, 2000, 34:15–18. 3. Moncrieff AA et al. Lead poisoning in children. Archives of Disease in Childhood, 1964, 39:1–13. 4. Glotzer DE, Freedberg KA, Bauchner H. Management of childhood lead poisoning: clinical impact and cost-effectiveness. Medical Decision Making, 1995, 15:13–24.