Pyridoxal-5-Phosphate

Newborn use only

2025

Alert	Hepatotoxicity has been reported with large doses, and the minimum dose of PLP required to control episodes of encephalopathy is to be prescribed.[1,2] Sudden respiratory arrest and profound hypotension can occur, therefore initiate treatment in a setting where resuscitation equipment is available.
Indication	Pyridox(am)ine 5'-phosphate oxidase (PNPO) deficiency.[2,3]
Action	Pyridoxal-5-phosphate (PLP) is the activated form of pyridoxine and eliminates the activation step that requires Pyridox(am)ine 5'-phosphate oxidase (PNPO).
Drug Type	Vitamin
Trade Name	Pydoxal, ISEI, Solgar P5P, Klaire – All these products are available in Australia via Special Access Scheme.
Presentation	Pyridoxal phosphate **powder** Pyridoxal phosphate 50mg **tablets** In-house Pharmacy preparation: Pyridoxal phosphate **capsules** in various strengths made by specialised hospital pharmacy
Dose	**To be prescribed only on the advice of paediatric neurologist/metabolic physician** **ANMF consensus (Refer to practice points section)** Pyridoxine should be tried first and PLP is only used if pyridoxine is ineffective. 30 mg/kg/day PO given in 4-6 divided doses. It may take up to 72 hours for an effect to be seen. Dose may be increased incrementally up to a maximum dose of 60mg/kg/day, but with an aim to minimise the dose and in particular use frequent small doses (with close monitoring of liver function tests).
Dose adjustment	Therapeutic hypothermia - No information. ECMO – No information. Renal impairment – No information. Hepatic impairment –Refer to alert, monitoring and evidence sections.
Maximum Dose	**ANMF consensus** - 60 mg/kg/day in 4-6 divided doses – the dosage should be titrated to the minimum dose required to prevent seizure in order to minimise potential PLP associated hepatotoxicity.
Total cumulative dose	
Route	Oral
Preparation	**Powder:** Weigh the required dose using a measuring scale and disperse in water and give immediately to prevent photodegradation. **Tablet:** Crush and disperse 50 mg tablet in 10 mL water of injections and administer required dose/potion immediately. Discard unused mixture. Make fresh preparation each time. **Capsule:** Individually prepared dose for each patient. Check with the hospital pharmacy providing the capsules.
Administration	**ORAL:** Give immediately after preparation (Rapid degradation to ineffective products may occur if mixture is left standing before administration) **IV:** While IV formulations of PLP are available, there are no safety data available for neonates. IV formulation is beyond the scope of this formulary and can only be decided by paediatric neurologist.
Monitoring	Baseline Liver function tests, coagulation profile and alpha-fetoprotein prior to commencement. **First dose:** respiratory rate, heart rate, blood pressure and oxygen saturation every 15 mins for 3 hours following first dose. **Ongoing:** Weekly Liver function tests for a few weeks until stable and monthly or as per paediatric neurologist. If LFTs are abnormal, check coagulation profile, alpha-fetoprotein and liver ultrasound (Expert advice). Monitor Creatine Kinase (for rhabdomyolysis).
Contraindications	Serious hypersensitivity to pyridoxal phosphate or any component of the formulation
Precautions	
Drug Interactions	Increases peripheral decarboxylation of levodopa and reduces the amount at site of action.
Adverse Reactions	Hypersensitivity symptoms such as rash. Apnoea, sudden respiratory arrest and profound hypotension, restlessness, drowsiness. Peripheral neuropathy, loss of strength and numbness of the limbs, muscle pain, rhabdomyolysis. Loss of appetite, vomiting, diarrhoea

	Elevated liver enzymes, cirrhosis, hepatocellular carcinoma
Overdose	AUSTRALIA: Contact the Poisons Information Centre on **13 11 26** for information on the management of overdose NEW ZEALAND: Contact the National Poisons Centre on **0800 764 766** for information on the management of overdose.
Compatibility	Fluids: Not applicable. PN at Y-site: Not applicable. Y-site: Not applicable.
Incompatibility	Fluids: Not applicable. PN at Y-site: Not applicable. Y site: Not applicable.
Stability	Use immediately after preparation as rapid photodegradation occur upon standing of mixture.
Storage	Store at room temperature below 25°C protected from moisture and light. Store in the original package.
Excipients	
Special Comments	
Evidence	**Background** **Pyridoxine 5' phosphate oxidase (PNPO) deficiency:** In PNPO deficiency, there are homozygous or heterozygous mutations on chromosome 17q21, resulting in a nonfunctional pyridoxine 5' phosphate oxidase enzyme (PNPO).[4] PNPO converts phosphorylated pyridoxine and pyridoxamine phosphate to pyridoxal 5' phosphate or PLP. PLP is a cofactor for many enzymes including glutamic acid decarboxylase. When concentrations are low, normal GABA synthesis is interrupted and hyperexcitability of neurons and seizures can occur. Diagnosis is typically confirmed with mutation analysis of the PNPO gene. Patients present somewhat differently than those with pyridoxine-related seizures. These patients are often born prematurely with seizures occurring more frequently in utero versus patients with pyridoxine-related seizures.[4] PNPO deficiency mimics neonatal hypoxic ischaemic encephalopathy (HIE) as many biomarkers of metabolic stress from seizures such as hyperammonemia, metabolic acidosis, hypoglycaemia may be present in both conditions. Clinical clues for the physician to consider IEMs/PNPO deficiency in the presence of clinical and radiological evidence of HIE are absence of maternal or perinatal event to justify the insult, difficulty in controlling the seizure, and recurrence of epileptic encephalopathy in the family with or without ischemic insult.[5] Treatment for PNPO deficiency requires either life-long pyridoxal phosphate (PLP) supplementation (60% of patients) or pyridoxine supplementation (40% of patients).[2,4-8] **Efficacy** There are case reports, case series, and an open label prospective study evaluating PLP in children.[2,4-6,8-12] Kuo et al, reported a preterm infant at 35 weeks and birthweight 1795 g, who developed seizures at hour 3 of life that were controlled with 40 mg IV PLP once followed by 10 mg IV every 6 hours. Seizures recurred when switching to oral pyridoxine. Repeated dosing of 50-mg IV PLP stopped seizures, which were subsequently controlled with 50 mg IV every 6 hours of PLP or 30 mg/kg/day. PLP was converted to oral form without breakthrough seizures.[12] Clayton et al described a male infant at 35 weeks' gestation who developed seizures on day 1 of life with no response to anticonvulsants or oral pyridoxine. Seizures stopped when oral 50 mg PLP was initiated. He was maintained on 30 mg/kg/day PLP.[11] In an open label prospective study, Wang et al studied the difference between pyridoxine and PLP in control of idiopathic intractable epilepsy in children. They diagnosed 94 (aged 8 months to 15 years) children with idiopathic intractable epilepsy for more than 6 months. All received intravenous PLP 10 mg/kg, then 10 mg/kg/day in 4 divided doses. If seizures recurred within 24 hours, another dose of 40 mg/kg was given, followed by 50 mg/kg/day in 4 divided doses. For those patients whose seizures were totally controlled, PLP was replaced by the same dose of oral pyridoxine. If the seizure recurred, intravenous PLP was infused followed by oral PLP 50 mg/kg/day. Eleven had dramatic and sustained responses to PLP; of these, five also responded to pyridoxine. Within 6 months of treatment with PLP or pyridoxine, 5 of the 11 patients were seizure free and had their previous antiepileptic medicine tapered off gradually. They suggested that PLP could replace pyridoxine in the treatment of intractable childhood epilepsy, particularly in the treatment of infantile spasms.[10] Hoffman et al reported 6 children with PNPO deficiency presented with neonatal epileptic encephalopathy.[8] Two were treated with PLP within the 1st month of life and showed normal development or moderate psychomotor retardation thereafter. Four children with late or no

	treatment died or showed severe mental handicap. Maximum doses used in these 2 children were 50 mg/kg/day and 100 mg/kg/day in 6 divided doses respectively. They suggested that, all neonates and infants with epileptic encephalopathy as well as prematurely born infants with hypoxic–ischaemic encephalopathy should receive a therapeutic trial with oral PLP (30 mg/kg/day in 3 doses for at least one day) in addition to pyridoxine (100 mg i.v. in a single dose, to be repeated and possibly increased to 500 mg in total) and folinic acid (3–5 mg/kg/day for 2-3 days). They suggested to carry out this trial in conjunction with appropriate metabolic investigations in urine, blood and CSF but should not be delayed until the results of the biochemical tests have been returned. They also noted that a single dose of PLP may not be conclusive as seizures can recur early and mask the positive response, and the recommended dose of PLP may not be enough for some children, and to gain complete seizure control it may be necessary to increase PLP administration to 4 to 6 times per day.[8] A case series was published by Cortes-Saladelafont et al on a small sample of 10 children treated with PLP in relation to normal-low PLP in CSF. They failed to show response to PLP in them, but only 1 child in this series had confirmed PNPO deficiency.[9] Porri et al reported a neonate presenting with seizures at 12 hours of age and was treated with 30 mg/kg of PLP after failure of multiple anticonvulsive therapy.[6] An Australian case series by Hatch et al, reported 4 confirmed cases of PNPO deficiency, promptly treated with PLP with subsequent favourable neurodevelopmental outcomes.[2] Case 1 was a neonate who developed status epilepticus by 1.5 h of age. He required intubation and ventilation and received loading doses of phenobarbitone, phenytoin and midazolam without seizure control being established. A trial of oral P5P 100 mg TDS was commenced at 40 h of age, after iv pyridoxine failed to result in clinical or EEG change. EEG improvement was seen by 3 days of treatment with PLP; seizures and neonatal encephalopathy progressively resolved. Subsequently a PNPO gene mutation was confirmed after 4 months of age, and P5P was continued at doses of up to 50 mg/kg/day. Case 2 was the younger sibling of case 1. Her mother had taken pyridoxine as part of a pregnancy multivitamin during the pregnancy (2.6 mg/day pyridoxine) and PLP during the last 3 days of the pregnancy. The infant was administered P5P from birth as a precaution given her sibling's diagnosis. No seizures or abnormal neurological behaviour was noted. An EEG, done at 24 h of age, was normal. Initial P5P dosing was 25 mg TDS (30 mg/kg/day). Neurodevelopmental assessment at 2.5 years was normal. In case 3 - seizures were first diagnosed at 4 weeks of age. Trials of pyridoxine, phenobarbitone, phenytoin and oxcarbazepine failed to control seizures. PLP (40 mg TDS) was commenced at 8 weeks of age with cessation of seizures and normalisation of the EEG. In case 4, intractable neonatal seizures occurred and multiple different anticonvulsants and pyridoxine were trialled, before commencing P5P at 28 days of age, with dose ranging from 50 to 100 mg/kg/day in divided doses. At age 2 years, the dose was reduced to 50-60 mg/kg/day in this case due to concerns of hepatotoxicity raised in a case report.[1] **Safety** Sudarsanam et al reported a case of an 8-year-old boy with PNPO deficiency, who developed cirrhosis following PLP treatment.[1] He developed seizures at 24 hours of age that were refractory to standard anticonvulsant therapy and a trial of pyridoxine but responded to PLP at 28 days of life. Management of seizures required escalation of PLP dose to 100 mg/kg/day by 2 years of age. Routine blood tests at this time showed significantly deranged liver function tests (LFTs). A wedge liver biopsy showed early cirrhosis with marked elevation of pyridoxal and pyridoxic acid levels in the liver sample. Despite extensive investigation, no cause other than PLP therapy could be identified for the cirrhosis. The PLP dose was weaned to 50 mg/kg/day before episodes of encephalopathy recurred. Concurrent with the reduction of his PLP dose, LFTs showed improvement. However, at 8 years of age, there is persistent evidence of hepatic fibrosis and early portal hypertension. They hypothesised hepatic toxicity due to PLP or its degradation products is the cause of cirrhosis in this boy.[1] Since this report, it has been suggested to treat PNPO deficiency with minimum dose of PLP required to prevent episodes of encephalopathy.[1,2] More recently reports have emerged of hepatocellular carcinoma in 2 patients with PNPO deficiency treated with PLP.[13,14] As such monitoring with liver function tests with hepatic imaging (ultrasound and MRI) if liver function tests are found to be abnormal.
Practice points	Expert advice (Dr Richard Webster): About 40% of patients with PNPO deficiency respond to pyridoxine. Pyridoxine is tried first before PLP. A starting dose of 30 mg/kg/day in 4-6 hourly divided doses is suggested with a maximum dose of 60mg/kg/day but with an aim to minimise the dose and in particular

	use frequent small doses. The recommendations in this formulary are based on international consensus guidelines being developed for PNPO deficiency.
References	1. Sudarsanam A, Singh H, Wilcken B, Stormon M, Arbuckle S, Schmitt B, et al. Cirrhosis associated with pyridoxal 5'-phosphate treatment of pyridoxamine 5'-phosphate oxidase deficiency. JIMD Reports, Volume 17. 2014:67-70. 2. Hatch J, Coman D, Clayton P, Mills P, Calvert S, Webster R, et al. Normal neurodevelopmental outcomes in PNPO deficiency: a case series and literature review. JIMD Reports, Volume 26. 2016:91-7. 3. Guerriero RM, Patel AA, Walsh B, Baumer FM, Shah AS, Peters JM, et al. Systemic manifestations in pyridox (am) ine 5'-phosphate oxidase deficiency. Pediatric neurology. 2017;76:47-53. 4. Cosnahan AS, Campbell CT. Inborn errors of metabolism in pediatric epilepsy. The Journal of Pediatric Pharmacology and Therapeutics. 2019;24(5):398-405. 5. Alghamdi M, Arold ST, Hasan H, Bashiri F. Pyridox (am) ine 5'-Phosphate Oxidase Deficiency: Severe Prenatal Presentation with Hypoxic Ischemic Encephalopathy. Journal of Pediatric Epilepsy. 2019;8(02):049-55. 6. Porri S, Fluss J, Plecko B, Paschke E, Korff CM, Kern I. Positive outcome following early diagnosis and treatment of pyridoxal-5'-phosphate oxidase deficiency: a case report. Neuropediatrics. 2014;45(01):064-8. 7. Guerin A, Aziz AS, Mutch C, Lewis J, Go CY, Mercimek-Mahmutoglu S. Pyridox (am) ine-5-phosphate oxidase deficiency treatable cause of neonatal epileptic encephalopathy with burst suppression: case report and review of the literature. Journal of child neurology. 2015;30(9):1218-25. 8. Hoffmann G, Schmitt B, Windfuhr M, Wagner N, Strehl H, Bagci S, et al. Pyridoxal 5'-phosphate may be curative in early-onset epileptic encephalopathy. Journal of Inherited Metabolic Disease: Official Journal of the Society for the Study of Inborn Errors of Metabolism. 2007;30(1):96-9. 9. Cortes-Saladelafont E, Molero-Luis M, Artuch R, Garcia-Cazorla A, Group HW, editors. Pyridoxal phosphate supplementation in neuropediatric disorders. Seminars in Pediatric Neurology; 2016: Elsevier. 10. Wang H, Kuo M, Chou M, Hung P, Lin K, Hsieh M, et al. Pyridoxal phosphate is better than pyridoxine for controlling idiopathic intractable epilepsy. Archives of disease in childhood. 2005;90(5):512-5. 11. Clayton P, Surtees R, DeVile C, Hyland K, Heales S. Neonatal epileptic encephalopathy. The Lancet. 2003;361(9369):1614. 12. Kuo M-F, Wang H-S. Pyridoxal phosphate-responsive epilepsy with resistance to pyridoxine. Pediatric neurology. 2002;26(2):146-7. 13. Webster R, Parayil Sankaran B, Bandodkar S, Stormon M, Thomas G, Shun A, Bowen DG, Fielder T, Barclay P, Khalil Y, Mills P, Clayton P, Bhattacharya K. Liver transplantation in PNPO deficiency: management challenges and biological lessons. Submitted Journal of Inherited Metabolic Disease May 2025. 14. De Liso P, Webster R, Plecko B, Vigevano F. Hepatocellular carcinoma in two unrelated patients with PNPO Deficiency Epilepsy: a risk of long-term Pyridoxal-5'-Phosphate therapy? In press European Journal of Child Neurology May 2025.

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Authors Contribution of the current version

Author/s	Srinivas Bolisetty, Richard Webster, Mohammad Irfan Azeem, Bhavesh Mehta
Evidence Review	Srinivas Bolisetty, Richard Webster
Expert review	Dr Richard Webster (Paediatric Neurologist, Sydney Children's Hospital Network (SCHN)
Nursing Review	Renae Gengaroli
Pharmacy Review	Mohammad Irfan Azeem

ANMF Group contributors	Bhavesh Mehta, Nilkant Phad, Amber Seigel, Jutta Van Den Boom, Rebecca Barzegar, Rebecca O'Grady, Michelle Jenkins, Thao Tran, Cindy Chen, Susannah Brew, Kerrie Knox, Bryony Malloy, Renae Gengaroli, Samantha Hassall, Celia Cunha Brites, Tiffany Kwan
Final editing	Dr Richard Webster, Mohammad Irfan Azeem, Srinivas Bolisetty
Electronic version	Cindy Chen, Ian Callander
Facilitator	Srinivas Bolisetty

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