Arginine (L-Arginine) 2025

Newborn use only

Alert	**Caution: overdose can be fatal in children.**
Indication	Urea cycle defects (**except Arginase deficiency**)
Action	In patients with urea cycle disorders, exogenous administration of arginine replenishes arginine.
Drug Type	Amino acid
Trade Name	Arginine hydrochloride (Phebra 60%) 15g/25mL injection, Arginine oral solution: multiple brands, Arginine oral powder.
Presentation	**IV:** Arginine hydrochloride 15g/25mL injection, **ORAL:** Argine 300mg/mL powder for oral solution; Arginine oral powder 500mg of arginine/4g sachet; Arginine oral powder 2g of arginine/4g sachet. **NOTE:** Facilities providing specialised metabolic services may have specific instructions to bedside nurses on combined IV preparations of sodium benzoate, L-arginine and/or sodium phenylbutyrate. Refer to preparation section.
Dose	**To be prescribed only on the advice of paediatric metabolic specialists/paediatrician specialised in metabolic disorders.** **Sodium benzoate and L-arginine are generally infused together. A combined infusion preparation is available (see preparation section)** **Rarely, Sodium benzoate, L- arginine and sodium phenylbutyrate can also be infused together. A combined infusion preparation is available (see preparation section)** **IV for acute hyperammonaemia (ANMF consensus)[1,2]** Commence loading dose at 250 (-400) mg/kg over 90–120 minutes, followed by maintenance dose at 250 mg/kg daily given as a continuous IV infusion over 24 hours (preferred) or rarely, on the advice of paediatric metabolic specialist, as intermittent IV infusions in 4 divided doses. Adjust dose according to response. Change to oral route when stable. **Note:** Citrullinaemia or arginosuccinic aciduria: Higher doses have been used (up to 600 mg/kg loading dose, then 600 mg/kg daily as a continuous infusion or in 4 divided doses). **ORAL Maintenance treatment (ANMF consensus)[1,2]** 250 mg/kg daily in 3 or 4 doses. Adjust dose according to response. Citrullinaemia or arginosuccinic aciduria: 300-600 mg/kg daily may be needed.
Dose adjustment	Therapeutic hypothermia – no information ECMO – no information Renal impairment – use with caution; use may lead to life-threatening hyperkalaemia Hepatic impairment – use with caution; use may lead to life-threatening hyperkalaemia
Maximum Dose	Load 600 mg/kg followed by a continuous IV infusion of 600mg/kg/day
Route	**IV or Oral**
Preparation	**Load / maintenance** **Arginine infusion:** Draw up 4.2 mL (2500mg) of L-arginine and add 45.8 mL of glucose 10% to make a final volume of 50 mL with a concentration of 50 mg/mL. **Combined Arginine and sodium benzoate infusion:** Draw up 4.2 mL (2500 mg) of L-arginine hydrochloride and 12.5 mL (2500 mg) of sodium benzoate and add 33.3 mL of glucose 10% to make a final volume of 50 mL with a concentration of 50 mg/mL of sodium benzoate and L-arginine each. **Combined Arginine, sodium benzoate and sodium phenylbutyrate infusion:** Draw up 4.2 mL (2500mg) of L-arginine hydrochloride, 12.5 mL (2500mg) of sodium benzoate and 12.5 mL of sodium phenylbutyrate and add 20.8 mL of glucose 10% to make a final volume of 50 mL with a concentration of 50 mg/mL of L-arginine, sodium benzoate, and sodium phenylbutyrate each.

Administration	IV: Infuse via central venous line (preferred). However, it can be administered via peripheral venous route. Extravasation via peripheral venous route can cause cutaneous necrosis.[3]
Monitoring	Serum electrolytes, urea, glucose, plasma ammonia and amino acids, acid base status, infusion site.
Contraindications	Hypersensitivity to arginine or any component of the formulation
Precautions	Vesicant, irritant and Hypertonic: extravasation may result in skin necrosis. Faster infusion rates may result in local irritation, flushing, nausea, or vomiting.
Drug Interactions	Arginine may potentiate the hypotensive effect of blood pressure lowering agents
Adverse Reactions	Risk of extravasation injury from infusion through peripheral venous route. Hyperchloremic acidosis. Systemic hypotension with large doses.
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:** Glucose 5%, Glucose 10%, Sodium chloride 0.9%. Sodium benzoate, L-arginine and sodium phenylbutyrate can be mixed together (ANMF consensus). **PN at Y-site:** No information. No information on lipid emulsions.[8] **Y-site:** No information.
Incompatibility	No information.
Stability	
Storage	Store at room temperature.
Excipients	IV formulation: water for injection 300mg/mL powder for oral solution: NIL Arginine oral powder 500mg/4g and 2g/4g sachets: arginine + carbohydrate
Special Comments	
Evidence	**Background** Ammonia is the nitrogen waste product from protein catabolism. Ammonia is present in all body fluids and exists primarily as ammonium ion at physiologic pH. Ammonia is toxic when present in high concentrations. Hyperammonemia is defined as a blood ammonia concentration greater than about 100 micromol/L in neonates or 50 micromol/L in children and adults (precise cut-offs vary, depending on individual laboratory normative ranges).[4] Hyperammonemia refers to a clinical condition characterized by elevated serum ammonia levels and manifests with hypotonia, seizures, emesis, and abnormal neurologic changes (including stupor).[5] Patients with urea cycle defects (UCD), organic acidemias, fatty acid oxidation defects, Reye syndrome can all present with elevations in ammonia. Hyperammonemia is the hallmark of UCDs with peak ammonia concentrations >500 µmol/L in most neonatal patients at presentation.[2] In urea cycle defects (UCD), nitrogen removal is blocked, and nitrogen accumulates in the form of ammonia, causing acute episodes of hyperammonemia.[6] Hyperammonaemia can also be caused by acquired conditions such as total parenteral nutrition, liver failure and urinary tract infections due to protease sp.[4] Reducing ammonia production can be achieved with IV L-arginine and nitrogen-removing agents (e.g., sodium phenylacetate and sodium benzoate). L-arginine is a semi-essential amino acid that plays critical physiological roles in muscle development and ammonia detoxification. Arginine is therapeutically useful in many life-threatening inborn errors of metabolism including UCD, MELAS syndrome and mitochondrial encephalopathies. Patients with UCD (except Arginase deficiency I) have low serum arginine levels and need this amino acid to be replaced, Arginine therapy helps prevent protein catabolism in the latter disorders.[5] Therapeutic arginine is also known to improve endogenous nitric oxide production and being evaluated for various conditions including pulmonary hypertension.[7] **Efficacy** A 1980 report by Batshaw et al published the relative effectiveness of exchange transfusion, peritoneal dialysis, arginine, and sodium benzoate in 31 children with congenital urea cycle enzymopathies. When NaBZ (250 mg/kg/day) was used during 8 episodes of hyperammonaemic coma, 6 patients responded with a significant decrease in plasma ammonium. All children with UCD showed hypoargininaemia. The

	mean arginine value was 18 ± 2 µM. In response to arginine supplementation (2 to 4 mmol/kg/day) plasma arginine concentrations returned to normal in all but one case.[4] In another study by Batshaw et al, 26 patients were treated with IV NaBZ (250 mg/kg loading dose, followed by 250 to 500 mg/kg per day continuous infusion) and arginine hydrochloride (800 mg/kg loading dose, followed by 200 to 800 mg/kg/day) during acute neonatal hyperammonemia. PD was required during neonatal hyperammonaemic coma episodes in 20 of 23 patients. They suggested that that alternative pathway therapy (NaBZ and arginine supplementation), combined with dietary restriction of protein and provision of supplemental calories in an amount no less than 100 kcal/kg/day, can prolong survival and improve clinical outcome in children who have UCDs.[3] **Guidelines** **2019 European expert panel consensus:** In hyperammonemia, L-arginine to be given as IV in glucose 10% at 250(-400) mg/kg (1–2 mmol/kg) as bolus in 90-120 minutes, then maintenance 250 mg/kg/day (1.2 mmol/kg/day).[2] ANMF consensus is to adopt these guidelines. **Pharmacokinetics** Oral L-arginine supplementation cannot sufficiently elevate the plasma levels of arginine due to the presence of arginase in intestinal enterocytes and the high first-pass metabolism of L-arginine to ornithine and urea by the liver arginases. Moreover, higher levels of circulating L-arginine induce arginases in most of the tissues resulting in rapid L-arginine clearance. L-citrulline, a natural precursor of L-arginine can be a better substitute of L-arginine supplementation because it bypasses hepatic first-pass metabolism and can be converted to L-arginine specifically within the tissues.[7] **Safety** Arginine, in large amounts, can accumulate and result in the production of large quantities of nitric oxide, which is a potent vasodilator and thus can lead to symptomatic hypotension.[5] Extravasation via peripheral venous route can cause severe cutaneous necrosis.[3]
Practice points	Sydney Children's Hospital Network Metabolic team – Often, arginine, sodium benzoate and sodium phenylbutyrate are prepared and co-infused together as a combined metabolic infusion.
References	1. Matsumoto S, Häberle J, Kido J, Mitsubuchi H, Endo F, Nakamura K. Urea cycle disorders—update. Journal of human genetics. 2019;64(9):833-47. 2. Häberle J, Burlina A, Chakrapani A, Dixon M, Karall D, Lindner M, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders: first revision. Journal of inherited metabolic disease. 2019;42(6):1192-230. 3. Mew A, Simpson KL, Gropman AL, Lanpher BC, Chapman KA, Summar ML. Urea cycle disorders overview. 2017. 4. Niemi A-K, Enns GM. Pharmacology review: sodium phenylacetate and sodium benzoate in the treatment of neonatal hyperammonemia. NeoReviews. 2006;7(9):e486-e95. 5. Auron A, Brophy PD. Hyperammonemia in review: pathophysiology, diagnosis, and treatment. Pediatric nephrology. 2012;27:207-22. 6. Husson M-C, Schiff M, Fouilhoux A, Cano A, Dobbelaere D, Brassier A, et al. Efficacy and safety of iv sodium benzoate in urea cycle disorders: a multicentre retrospective study. Orphanet journal of rare diseases. 2016;11:1-8. 7. Rashid J, Kumar SS, Job KM, Liu X, Fike CD, Sherwin CMT. Therapeutic Potential of Citrulline as an Arginine Supplement: A Clinical Pharmacology Review. Paediatr Drugs. 2020;22(3):279-93. 8. MerativeTM Micromedex® Complete IV Compatibility (electronic version). Merative, Ann Arbor, Michigan, USA. Available at: https://www.micromedexsolutions.com/ (cited: Feb/26/2025).

VERSION/NUMBER	DATE
Original 1.0	**29/05/2025**
REVIEW	**29/05/2030**

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Citation for the current version

Bolisetty S, Azeem MI, Mehta B, Ellaway C, Balasubramaniam S, Gengaroli R, Phad N, Seigel A, Barzegar R, van den Boom J, O'Grady R, Jenkins M, Tran T, Chen C, Brew S, Malloy B, Hassall S, Brites CC, Kwan T, Callander I. Arginine. Consensus formulary by the Australasian Neonatal Medicines Formulary group. Version 1, dated 29 May 2025. www.anmfonline.org