Sodium Benzoate
Newborn use only

2025

Alert	Available through Special Access Scheme only. **Caution: Overdose can be fatal in children.**
Indication	Acute hyperammonaemia
Action	Sodium benzoate is an ammonia scavenging medication. It lowers serum ammonia by diverting blood urea nitrogen to hippurate nitrogen by conjugating with glycine. Hippurate nitrogen can be readily excreted in urine.[1]
Drug Type	Ammonia scavenger
Trade Name	Amzoate
Presentation	**IV:** 2g/10mL injection. Clear, colourless solution **ORAL:** Sodium benzoate (Amzoate) (SAS) 500mg **tablet**. In-house Pharmacy preparation: Sodium Benzoate individual dose **capsules** are compounded by specialised hospital pharmacy dept. 100 mg/mL **liquid** (In New Zealand)
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)[2-4]** Commence loading dose at 250 mg/kg over 90–120 minutes, followed by maintenance dose at 250 mg/kg daily given as a continuous infusion over 24 hours (preferred) or rarely, on the advice of paediatric metabolic specialist, intermittent infusions in 4 divided doses. Adjust dose according to response - Maximum 500 mg/kg daily. Any dose higher than 500 mg/kg/daily is at the discretion of paediatric metabolic specialist. Change to oral route when stable. **ORAL Maintenance treatment** 250 mg/kg daily in 3 or 4 doses. Adjust dose according to response - Maximum 500 mg/kg daily.
Dose adjustment	Therapeutic hypothermia - No information. ECMO – No information. Renal impairment – No information. Hepatic impairment – In newborns with unconjugated hyperbilirubinemia, close monitoring is required as unconjugated fraction can rise with sodium benzoate therapy.[5]
Maximum Dose	500 mg/kg/day
Route	IV ORAL
Preparation	**IV** **Load / maintenance** **20mL syringe** **Sodium benzoate single infusion preparation** Draw up 5 mL (1000 mg) of sodium benzoate and add 15 mL of glucose 10% to make a final volume of 20 mL with a concentration of 50 mg/mL. **Sodium benzoate and L-arginine combined infusion preparation**

	Draw up 5 mL (1000 mg) of sodium benzoate and 1.7 mL (~1000mg) of L-arginine hydrochloride and add 13.3 mL of glucose 10% to make a final volume of 20 mL with a concentration of 50 mg/mL of sodium benzoate and L-arginine each. **Sodium benzoate, L-arginine and sodium phenylbutyrate combined infusion preparation** Draw up 5mL (1000 mg) of sodium benzoate, 1.7 mL (~1000 mg) of L-arginine hydrochloride and 5 mL (1000 mg) of sodium phenylbutyrate and add 8.3 mL of glucose 10% to make a final volume of 20 mL with a concentration of 50 mg/mL of sodium benzoate, L-arginine and sodium phenylbutyrate each. **50mL Syringe** **Sodium benzoate single infusion preparation** Draw up 12.5 mL (2500 mg) of sodium benzoate and add 37.5 mL of glucose 10% to make a final volume of 50 mL with a concentration of 50 mg/mL. **Sodium benzoate and L-arginine combined infusion preparation** Draw up 12.5 mL (2500 mg) of sodium benzoate and 4.2 mL (~2500 mg) of L-arginine hydrochloride 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. **Sodium benzoate, L-arginine and sodium phenylbutyrate combined infusion preparation** Draw up 12.5 mL (2500 mg) of sodium benzoate, 4.2 mL (~2500 mg) of L-arginine hydrochloride and 12.5 mL of sodium phenylbutyrate (2500 mg) and add 20.8 mL of glucose 10% to make a final volume of 50 mL with a concentration of 50 mg/mL of sodium benzoate, L-arginine and sodium phenylbutyrate each. **ORAL** Crush and dissolve 500mg tablet in 5 mL of water to make 100 mg/mL oral liquid, give required dose immediately, discard remaining liquid, Prepare a fresh batch for each dose.
Administration	**IV** Administer via central line (preferred) or large peripheral vein.[6] Loading dose to be administered over 90 – 120 minutes. Maintenance dose to be infused over 24 hours **ORAL** Give with meals.
Monitoring	Plasma/serum ammonia (suggested level <100 micromol/L, however, to be decided by the specialist paediatric metabolic team) Blood gas, glucose and electrolytes, and liver function tests Plasma amino acids.
Contraindications	Hypersensitivity to sodium benzoate
Precautions	Use with caution in neonates with unconjugated hyperbilirubinemia, but metabolic condition may itself have caused hyperbilirubinemia Use with caution in neonates with metabolic acidosis, but metabolic condition may itself have caused metabolic acidosis. Use with caution in neonates with hypernatremia
Drug Interactions	Corticosteroids, sodium valproate, penicillins may reduce the efficacy of sodium benzoate.
Adverse Reactions	Avoid extravasation Rapid infusion may cause flushing, nausea, vomiting, numbness, headache, and local venous irritation Worsening of unconjugated hyperbilirubinemia, Kernicterus Vomiting, anorexia, irritability, lethargy ORAL – Gastritis and mucositis.
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 10%[7], glucose 5%, sodium chloride 0.45%, sodium chloride 0.9%. Glucose is the preferred diluent. (see special comments) PN at Y-site: No information.[7] No information on lipid emulsions.[7] Y-site: Arginine, levocarnitine, sodium phenylbutyrate No information on other drugs.[7]
Incompatibility	Fluids: No information. No information on lipid emulsions.[7] PN at Y-site: No information. Y site: No information.
Stability	Diluted solution should be used immediately. Stable for 24 hours at room temperature
Storage	Store at room temperature (<25^{0}C)
Excipients	Di sodium edetate
Special Comments	Metabolic experts may co-infuse sodium benzoate with L-arginine and sodium phenylbutyrate in G10W. Each 1g of sodium benzoate contains 7 mmol of sodium.
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. 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). A 5- to 10-fold increase in blood ammonia concentration usually is toxic to the nervous system.[1] 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 be caused by inborn errors of metabolism or acquired conditions such as total parenteral nutrition.[1] Sodium benzoate is an ammonia scavenging medication. It lowers serum ammonia concentrations by the activation of a non-urea cycle pathway of ammonia removal.[5] It lowers serum ammonia by diverting blood urea nitrogen to hippurate nitrogen by conjugating with glycine. Hippurate nitrogen can be readily excreted in urine.[1] **Efficacy** Batshaw et al studied the relative effectiveness of exchange transfusion, peritoneal dialysis, arginine, and sodium benzoate in 31 patients with congenital urea cycle enzymopathies. When sodium benzoate (250 mg/kg/day) was used during 8 episodes of hyperammonaemic coma, 6 patients responded with a significant decrease in plasma ammonium.[4] In another study by Batshaw et al, 26 patients were treated with IV sodium benzoate (250 mg/kg loading dose, followed by 250 to 500 mg/kg/day continuous infusion) and arginine hydrochloride (800 mg/kg loading dose, followed by 200 to 800 mg/kg/day) during acute neonatal hyperammonemia. Peritoneal dialysis was required during neonatal hyperammonaemic coma episodes in 20 of 23 patients. They suggested that alternative pathway therapy (sodium benzoate and arginine), 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] A 10-year retrospective multicentre study in 61 patients (25 were neonates) treated for UCD in 6 French reference centres reported that sodium benzoate was effective and safe in acute episodes of hyperammonaemia.[6] A loading dose of IV sodium benzoate (median 250 mg/kg over 2 h) was administered for 41/95 acute episodes. The median maintenance dose was 246.1 mg/kg/day, administered via peripheral venous infusion in all cases except one via a central line. The total median duration of IV sodium benzoate treatment per episode was 2 days (0–13 days). A decrease in ammonium level to ≤ 100 µmol/L was obtained in 92.8 % of episodes. Five patients required another treatment for hyperammonemia (sodium phenylacetate + sodium benzoate, haemofiltration). Local side effects (local effusion and oedema) have been reported in 18 instances.[6] **Guidelines** 2019 European expert panel consensus: In hyperammonemia, IV sodium benzoate to be given as IV in glucose 10% at 250 mg/kg as bolus in 90-120 minutes, then maintenance 250-500 mg/kg/day.[8] British Inherited Metabolic Disease Group: The standard dose is 250 mg/kg/d in divided doses. This may be increased to 500 mg/kg/d in an emergency.[9] **Pharmacokinetics** More than half of the administered benzoate is converted to hippurate. Hippurate is effectively cleared by kidneys.[5]

	Safety Sodium benzoate is toxic only at a plasma concentrations >2 mmol/L.[8] In jaundiced newborns with unconjugated hyperbilirubinemia, close monitoring is required as unconjugated fraction can rise with sodium benzoate therapy.[5] The other common side effects are nausea and vomiting. Tinnitus and visual disturbance have also been recorded in adults. However, side effects may be underrecognized as it can be difficult to distinguish those of benzoate toxicity and of hyperammonaemia.[10] Sodium benzoate can cause depletion of Acyl-CoA with secondary mitochondrial dysfunction, and N-acetyl glutamate (NAG). Sodium benzoate oral preparations can cause mucositis or gastritis, therefore oral dosages with meals and abundant fluids are recommended.[8]
Practice points	Gastro-intestinal side-effects may be reduced by giving smaller doses more frequently.
References	1. Niemi A-K, Enns GM. Pharmacology review: sodium phenylacetate and sodium benzoate in the treatment of neonatal hyperammonemia. NeoReviews. 2006;7(9):e486-e95. 2. Häberle J, Boddaert N, Burlina A, Chakrapani A, Dixon M, Huemer M, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders. Orphanet journal of rare diseases. 2012;7:1-30. 3. Batshaw ML, Brusilow S, Waber L, Blom W, Brubakk AM, Burton BK, et al. Treatment of inborn errors of urea synthesis: activation of alternative pathways of waste nitrogen synthesis and excretion. New England Journal of Medicine. 1982;306(23):1387-92. 4. Batshaw ML, Brusilow SW. Treatment of hyperammonemic coma caused by inborn errors of urea synthesis. The journal of Pediatrics. 1980;97(6):893-900. 5. Green TP, Marchessault RP, Freese DK. Disposition of sodium benzoate in newborn infants with hyperammonemia. The Journal of pediatrics. 1983;102(5):785-90. 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. MerativeTM Micromedex® Complete IV Compatibility (electronic version). Merative, Ann Arbor, Michigan, USA. Available at: https://www.micromedexsolutions.com/ (cited: Feb/26/2025). 8. 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. 9. British Inherited Metabolic Disease Group. Medicines used for the tretament of hyperammonaemia. https://bimdg.org.uk/wp-content/uploads/2024/12/Paeds_NH3_meds_NEW-DEC-VERSION.pdf. Downladed on 26 February 2025. 10. Feillet F, Leonard J. Alternative pathway therapy for urea cycle disorders. Journal of inherited metabolic disease. 1998;21(Suppl 1):101-11.

VERSION/NUMBER	DATE
Original 1.0	**29/05/2025**
Current 1.0 (minor errata)	**5/02/2026**
REVIEW	**29/05/2030**

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Citation for the current version
Australasian Neonatal Medicines Formulary (ANMF). Sodium benzoate. Version number: 1 (minor errata). Date of publication 5/02/2026. https://www.anmfonline.org/