Safety Data Sheet

Sodium Phenylacetate and Sodium Benzoate Injection 10%/10%

Strength: 10% / 10% w/w (sterile), **Pack Size:** 50mL per vial

EMERGENCY OVERVIEW

Sodium Phenylacetate and Sodium Benzoate Injection 10%/10% is sterile concentrated, aqueous solution of sodium phenylacetate and sodium benzoate. It must be diluted with sterile 10% Dextrose Injection (D10W) before administration. Excipients generally considered to be non-toxic and non-hazardous in small quantities and under conditions of normal occupational exposure.

Section 1. Identification

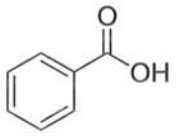
Identification of the product:

Product Name: Sodium Phenylacetate and Sodium Benzoate Injection 10%/10%

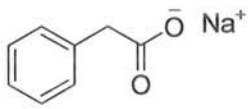
Formula:

a. $C_8 H_7 NaO_2$ (Sodium Phenylacetate)
b. $C_7 H_6O_2$ (Benzoic acid)
c. NaOH (Sodium Hydroxide)

Structure:



Benzoic Acid



Sodium Phenylacetate

Molecular Formula

a. $C_8 H_7 NaO_2$ (Sodium Phenylacetate)
b. $C_7 H_6O_2$ (Benzoic acid)
c. NaOH (Sodium Hydroxide)

Molecular Weight

a. 158.13 g/mole (Sodium Phenylacetate)
b. 122.12 g/mole(Benzoic acid)
c. 39.99 g/mole (Sodium Hydroxide)

Physical description

a. Sodium Phenylacetate is white to off-white powder
b. Benzoic Acid is white crystalline powder.
c. Sodium Hydroxide is available as small white pellets.

pKa

a. Sodium Phenylacetate: 4.31*
b. Benzoic Acid : 4.202**
c. Sodium Hydroxide : 13.8

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DESCRIPTION: sodium phenylacetate and sodium benzoate Injection 10% per 10% (a nitrogen binding agent), is a sterile, concentrated, aqueous solution of sodium phenylacetate and sodium benzoate. The pH of the solution is between 6 and 8. Sodiumphenylacetate is a crystalline, white to off-white powder with a strong, offensive odor. It is soluble in water. Sodium benzoate is awhite and odorless, crystalline powder that is readily soluble in water.

Potential Health Effects:

Acute Eye : May cause irritation.
Acute Skin : May cause irritation.
Acute Inhalation: May irritate the mucous membranes and upper respiratory tract. May cause allergic reactions.
Acute ingestion: None expected under anticipated use conditions.

Supplier / Manufacturer identification

Address : 1499 Lower Ferry Road, Ewing, New Jersey 08618-1414, USA
Contact for information: Tel.: 609-883-1135 Fax: 609-883-1137
Emergency Telephone No. Tel.: 609-883-1135

Manufactured For: Zydus Pharmaceuticals USA Inc.

Recommended use / Therapeutic Category: Indicated as adjunctive therapy in pediatric and adult patients for the treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle. During acute hyperammonemic episodes, arginine supplementation, caloric supplementation, dietary protein restriction, hemodialysis, and other ammonia lowering therapies should be considered.

Section 2. Hazard(s) Information

Dose and Administration

Recommended Dose

Sodium Phenylacetate and Sodium Benzoate Injection 10%/10% must be diluted with sterile 10% Dextrose Injection (D10W) before administration. The dilution and dosage of SODIUM PHENYLACETATE AND SODIUM BENZOATE INJECTION 10%/10% are determined by weight for neonates, infants and young children, and by body surface area for larger patients, including older children, adolescents, and adults **(Table 1).**

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Table 1: Dosage and administration

Patient Population	Components of infusion Solution SODIUM PHENYLACETATE AND SODIUM BENZOATE INJECTION 10%/10% must be diluted with sterile 10% Dextrose Injection at ≥ 25 mL/Kg before administration.		Dosage Provided		
	SODIUM PHENYLACETATE AND SODIUM BENZOATE INJECTION 10%/10%	Arginine HCL Injection, 10%	Sodium Phenylacetate	Sodium benzoate	Arginine HCL
Patients 0 to 20 kg:					
CPS and OTC Deficiency					
Dose Loading: over 90 t0 120 minutes Maintenance: over 24 hours	2.5 mL/kg	2 mL/kg	250 mg/kg	250 mg/kg	200 mg/kg
ASS and ASL Deficiency					
Dose Loading: over 90 t0 120 minutes Maintenance: over 24 hours	2.5 mL/kg	6 mL/kg	250 mg/kg	250 mg/kg	600 mg/kg
Patients > 20kg:					
CPS and OTC Deficiency					
Dose Loading: over 90 to 120 minutes Maintenance: over 24 hours	55 mL/m^2	2 mL/kg	5.5 g/m^2	5.5 g/m^2	200 mg/kg
ASS and ASL Deficiency					
Dose Loading: over 90 t0 120 minutes Maintenance: over 24 hours	55 mL/m^2	6 mL/kg	5.5 g/m^2	5.5 g/m^2	600 mg/kg

Administration

Sodium Phenylacetate and Sodium Benzoate Injection 10%/10% is a concentrated solution and must be diluted before intravenous administration via a central venous catheter. Administration through a peripheral intravenous catheter may cause burns. Sodium Phenylacetate and Sodium Benzoate Injection 10%/10% may not be administered by any other route. Sodium Phenylacetate and Sodium Benzoate Injection 10%/10% should be administered as a loading dose infusion over 90 to 120 minutes, followed by the same dose repeated as a maintenance infusion administered over 24 hours. Because of prolonged plasma levels achieved by phenylacetate in pharmacokineticstudies, repeat loading doses of Sodium Phenylacetate and Sodium Benzoate Injection 10%/10% should not be administered. Maintenance infusions may be continued until elevated plasma ammonia levels have been normalized or the patient can tolerate oral nutrition and medications.

An antiemetic may be administered during Sodium Phenylacetate and Sodium Benzoate Injection 10%/10% infusion to aid control of infusion-associated nausea and vomiting. Administration of analogous oral drugs, such as sodium phenylbutyrate, should be terminated prior to Sodium Phenylacetate and Sodium Benzoate Injection 10%/10% infusion.

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Sodium Phenylacetate and Sodium Benzoate Injection 10%/10% infusion should be started as soon as the diagnosis of hyperammonemia is made. Treatment of hyperammonemia also requires caloric supplementation and restriction of dietary protein. Non-protein calories should be supplied principally as glucose (8–10 mg/kg/min) with an intravenous fat emulsion added. Attempts should be made to maintain a caloric intake of greater than 80 kcal/kg/day. During and after infusion of Sodium Phenylacetate and Sodium Benzoate Injection 10%/10% , ongoing monitoring of the following clinical laboratory values is crucial: plasma ammonia, glutamine, quantitative plasma amino acids, blood glucose, electrolytes, venous or arterial blood gases, AST and ALT.

On-going monitoring of the following clinical responses is also crucial to assess patient response to treatment: neurological status, Glasgow Coma Scale, tachypnea, CT or MRI scan or fundoscopic evidence of cerebral edema, and/or of gray matter and white matter damage. Hemodialysis should be considered in patients with severe hyperammonemia or who are not responsive to Sodium Phenylacetate and Sodium Benzoate Injection 10%/10% administration. In the non-neonatal study patient population treated with Sodium Phenylacetate and Sodium Benzoate Injection 10%/10%, dialysis was required in 13% of hyperammonemic episodes. Standard hemodialysis was the most frequently used dialysis method. High levels of ammonia can be reduced quickly when Sodium Phenylacetate and Sodium Benzoate Injection 10%/10% is used with hemodialysis, as the ammonia-scavenging of Sodium Phenylacetate and Sodium Benzoate Injection 10%/10% suppresses the production of ammonia from catabolism of endogenous protein and hemodialysis eliminates the ammonia and ammonia conjugates.

Sodium Phenylacetate and Sodium Benzoate Injection 10%/10% solutions are physically and chemically stable for up to 24 hours at room temperature and room lighting conditions. No compatibility information is presently available for Sodium Phenylacetate and Sodium Benzoate Injection 10%/10% infusion solutions except for Arginine HCl Injection, 10%, which may be mixed in the same container as Sodium Phenylacetate and Sodium Benzoate Injection 10%/10%. Other infusion solutions and drug products should not be administered together with Sodium Phenylacetate and Sodium Benzoate Injection 10%/10% infusion solution. Sodium Phenylacetate and Sodium Benzoate Injection 10%/10% solutions may be prepared in glass and PVC containers.

ADVERSE REACTIONS:

Based on literature , adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The safety data were obtained from 316 patients who received Sodium Phenylacetate and Sodium Benzoate Injection 10%/10% as emergency (rescue) or prospective treatment for hyperammonemia as part of an uncontrolled, open-label study. The study population included patients between the ages of 0 to 53 years with a mean (SD) of 6.2 (8.54) years; 51% were male and 49% were female who had the following diagnoses: OTC (46%), ASS (22%), CPS (12%), ASL (2%), ARG (< 1%), THN (< 1%), and other (18%).

Adverse reactions were reported with similar frequency in patients with OTC, ASS, CPS, and diagnoses categorized as "other."Nervous system disorders were more frequent in patients with OTC and CPS, compared with patients with ASS and patients with "other" diagnoses. Convulsions and mental impairment were reported in patients with OTC and CPS. These observations are consistent with literature reports that patients with enzyme deficiencies occurring earlier in the urea cycle (i.e., OTC and CPS) tend to be more severely affected.

Adverse reactions profiles differed by age group. Patients 30 days of age had more blood and lymphatic system disorders and vascular disorders (specifically hypotension), while patients > 30 days of age had more gastrointestinal disorders (specifically nausea, vomiting and diarrhea). Less common adverse reactions (< 3% of patients) that are characterized as severe are listed below by body system.

BLOOD AND LYMPHATIC SYSTEM DISORDERS: coagulopathy, pancytopenia, thrombocytopenia

CARDIAC DISORDERS: atrial rupture, bradycardia, cardiac or cardiopulmonary arrest/failure, cardiogenic shock, cardiomyopathy, pericardial effusion.

EYE DISORDERS: blindness

GASTROINTESTINAL DISORDERS: abdominal distension, gastrointestinal hemorrhage

GENERAL DISORDERS AND ADMINISTRATION-SITE CONDITIONS: asthenia, brain death, chest pain, multiorgan failure, edema.

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HEPATOBILIARY DISORDERS: cholestasis, hepatic artery stenosis, hepatic failure/hepatotoxicity, jaundice.
INFECTIONS AND INFESTATIONS: sepsis/septic shock
INJURY, POISONING AND PROCEDURAL COMPLICATIONS: brain herniation, subdural hematoma, overdose
INVESTIGATIONS: blood carbon dioxide changes, blood glucose changes, blood pH increased, cardiac output decreased, pCO2 changes, respiratory rate increased
METABOLISM AND NUTRITION DISORDERS: alkalosis, dehydration, fluid overload/retention, hypoglycemia, hyperkalemia, hypernatremia, alkalosis, tetany NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED: hemangioma acquired

NERVOUS SYSTEM DISORDERS: areflexia, ataxia, brain infarction, brain hemorrhage, cerebral atrophy, clonus, depressed level of consciousness, encephalopathy, nerve paralysis, intracranial pressure increased, subdural hematoma, tremor
PSYCHIATRIC DISORDERS: acute psychosis, aggression, confusional state, hallucinations
RENAL AND URINARY DISORDERS: anuria, renal failure, urinary retention
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS: acute respiratory distress syndrome, dyspnea, hypercapnia, hyperventilation, Kussmaul respiration, pneumonia aspiration, pneumothorax, pulmonary hemorrhage, pulmonary edema, respiratory acidosis or alkalosis, respiratory arrest/failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS: alopecia, blister, pruritis generalized, rash, urticaria
VASCULAR DISORDERS: flushing, hemorrhage, hypertension, phlebothrombosis/thrombosis.

Over Dose Effect: In case of overdose of Sodium Phenylacetate and Sodium Benzoate Injection , discontinue the drug and institute appropriate emergency medical monitoring and procedures. In severe cases, the latter may include hemodialysis (procedure of choice) or peritoneal dialysis (when hemodialysis is unavailable).

Causes of death in these patients included cardiorespiratory failure/arrest (6 patients), hyperammonemia (3 patients), increased intracranial pressure (2 patients), pneumonitis with septic shock and coagulopathy (1 patient), error in dialysis procedure (1 patient), respiratory failure (1 patient), intractable hypotension and probable sepsis (1 patient), and unknown (1 patient). Additionally, other signs of intoxication may include obtundation (in the absence of hyperammonemia), hyperventilation, a severe compensated metabolic acidosis, perhaps with a respiratory component, large anion gap, hypernatremia and hyperosmolarity, progressive encephalopathy, cardiovascular collapse, and death.

CONTRAINDICATIONS: None.

PRECAUTIONS

Management of Acute Hyperammonemia Any episode of acute symptomatic hyperammonemia should be treated as a life-threatening emergency. Uncontrolled hyperammonemia can rapidly result in brain damage or death, and prompt use of all therapies necessary, including hemodialysis, to reduce ammonia levels is essential.
Hyperammonemic coma (regardless of cause) in the newborn infant should be aggressively treated while the specific diagnosis is pursued. Hemodialysis should be promptly initiated in all newborn patients. A blood flow rate of 150 mL/min/m2 should be targeted (ammonia clearance [mL/min] is similar to the blood flow rate [mL/min] through the dialyzer). Clearance of ammonia is approximately ten times greater by hemodialysis than by peritoneal dialysis or hemofiltration. Exchange transfusion is ineffective in the management of hyperammonemia. Hemodialysis may be repeated until the plasma ammonia level is stable at normal or near normal levels.
Hyperammonemia due to urea cycle disorders should be managed in coordination with medical personnel experienced in metabolic disorders. Ongoing monitoring of plasma ammonia levels, neurological status, laboratory tests, and clinical response in patients receiving SODIUM PHENYLACETATE AND SODIUM BENZOATE INJECTION 10%/10% is crucial to assess patient response to treatment.
Decreased Potassium Levels
Because urine potassium loss is enhanced by the excretion of the non-reabsorbable anions, phenylacetylglutamine and hippurate, plasma potassium levels should be carefully monitored and appropriate treatment given when necessary.

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Conditions Associated with Fluid Overload

Sodium Phenylacetate and Sodium Benzoate Injection 10%/10% contains 30.5 mg of sodium per mL of undiluted product. Thus, Sodium Phenylacetate and Sodium Benzoate Injection 10%/10% should be used with great care, if at all, in patients with congestive heart failure or severe renal insufficiency, and in clinical states in which there is sodium retention with edema. Discontinue administration of Sodium Phenylacetate and Sodium Benzoate Injection 10%/10%, evaluate the patient, and institute appropriate therapeutic countermeasures if an adverse event occurs.

Extravasation

Administration must be through a central line. Administration through a peripheral line may cause burns. Bolus infusion flow rates are relatively high, especially for infants [*see Dosage and Administration (2)*]. Extravasation of Sodium Phenylacetate and Sodium Benzoate Injection 10%/10% into the perivenous tissues may lead to skin necrosis. If extravasation is suspected, discontinue the infusion and resume at a different infusion site, if necessary.

The infusion site must be monitored closely for possible infiltration during drug administration. Do not administer undiluted product.

Neurotoxicity of Phenylacetate

Because of prolonged plasma levels achieved by phenylacetate in pharmacokinetic studies, repeat loading doses of Sodium Phenylacetate and Sodium Benzoate Injection 10%/10% should not be administered. Additionally, neurotoxicity was reported in cancer patients receiving intravenous phenylacetate, 250–300 mg/kg/day for 14 days, repeated at 4-week intervals. Manifestations were predominantly somnolence, fatigue, and lightheadedness, with less frequent headaches, dysgeusia, hypoacusis, disorientation, impaired memory, and exacerbation of a pre-existing neuropathy.

The acute onset of symptoms upon initiation of treatment and reversibility of symptoms when the phenylacetate was discontinued suggest a drug effect.

Hyperventilation and Metabolic Acidosis

Due to structural similarities between phenylacetate and benzoate to salicylate, Sodium Phenylacetate and Sodium Benzoate Injection 10%/10% may cause side effects typically associated with salicylate overdose, such as hyperventilation and metabolic acidosis. Monitoring of blood chemistry profiles, blood pH and pCO2 should be performed.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Sodium Phenylacetate and Sodium Benzoate Injection 10%/10%. It is not known Sodium Phenylacetate and Sodium Benzoate Injection 10%/10%can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Thus, Sodium Phenylacetate and Sodium Benzoate Injection 10%/10% should be given to a pregnant woman only if clearly needed.

Section 3. Composition / information on ingredients

Component	Sodium Hydroxide, NF	Benzoic acid	Sodium Phenylacetate	Hydrochloric Acid, NF	Sterile Water for injection, USP
Exposure Limit	2 mg/m3	Not found	Not found	5 ppm Ceiling	Not found
CAS No.	1310-73-2	65-85-0	114-70-5	7647-01-0	7732-18-5

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Section 4. First aid measures

Overdose Treatment

As per FDA approved AMMONUL product Overdosage has been reported during Sodium Phenylacetate and Sodium Benzoate Injection 10%/10% treatment in urea cycle-deficient patients. All patients in the uncontrolled openlabel study were to be treated with the same dose of Sodium Phenylacetate and Sodium Benzoate Injection 10%/10%. However, some patients received more than the dose level specified in the protocol.

In 16 of the 64 deaths, the patient received a known overdose of Sodium Phenylacetate and Sodium Benzoate Injection 10%/10%. Causes of death in these patients included cardiorespiratory failure/arrest (6 patients), hyperammonemia (3 patients), increased intracranial pressure (2 patients), pneumonitis with septic shock and coagulopathy (1 patient), error in dialysis procedure (1 patient), respiratory failure (1 patient), intractable hypotension and probable sepsis (1 patient), and unknown (1 patient). Additionally, other signs of intoxication may include obtundation (in the absence of hyperammonemia), hyperventilation, a severe compensated metabolic acidosis, perhaps with a respiratory component, large anion gap, hypernatremia and hyperosmolarity, progressive encephalopathy, cardiovascular collapse, and death.

In case of overdose of AMMONUL, discontinue the drug and institute appropriate emergency medical monitoring and procedures. In severe cases, the latter may include hemodialysis (procedure of choice) or peritoneal dialysis (when hemodialysis is unavailable).

Section 5. Fire -fighting measures

Flash point: Not found

Upper Flammable Limit: Not found

Auto-IgnitionTemperature: Not found

Extinguishing Media: Water Spray, dry chemical, carbon dioxide or foam as appropriate for surrounding fire and material.

Fire and Explosion Hazard: This material is assumed to be combustible. As with all dry powders it is advisable to ground mechanical equipment in contact with the dry material to dissipate the potential build up of static electricity. Generally none anticipated for this aqueous product.

Fire fighting Procedure: As with all fires, evacuate personnel to a safe area. Fire fighter should use self-contained breathing equipment and protective clothing.

Section 6. Accidental Release Measures

Spill Response: Wear approved respiratory protection, chemically compatible gloves and protective clothing. Wipe up spillage or collect spillage using high efficiency vacuum cleaner. Avoid breathing dust. Place spillage in appropriately labelled container for disposal. Wash spill site.

Section 7. Handling and Storage

Storage: Store at 25°C (77°F), excursions permitted to 15° - 30°C (59°- 86°F).

Incompatibilities: Store according to label and/or product insert information. Store away from oxidizers, acids, and bases.

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Section 8. Exposure controls / personal protection

Respiratory Protection: Where respirators are deemed necessary to reduce or control occupational exposures, use NIOSH-approved respiratory protection and have an effective respirator program in place (applicable U.S. regulation OSHA 29 CFR 1910.134).

Skin protection: Protective laboratory coat, apron, or disposable garment. Chemically compatible gloves for handling solutions ensure that the glove material is protective against the solvent being used. Use handling practice that minimize natural rubber (latex) should use nitrile or other synthetic non-latex glove.
Use powdered latex gloves should be avoided to the risk of latex allergy.

Eye protection: Safety glasses with side shields are recommended. Face shields or goggles may be required if splash potential exists or if corrosive materials are present. Approved eye protection (e.g., bearing the ANSI Z87 or CSA stamp) is preferred. Maintain eyewash facilities in the work area.

Protective Clothing: Protective clothing is not normally necessary, however it is good practice to use apron.

Engineering Controls: Airborne exposure should be controlled primarily by engineering controls such as general dilution ventilation, local exhaust ventilation, or process enclosure. Local exhaust ventilation is
generally preferred to general exhaust because it can control the contaminant at its source, preventing dispersion into the work area. An industrial hygiene survey involving air monitoring may be used to determine the effectiveness of engineering controls. Effectiveness of engineering controls intended for use with highly potent materials should be assessed by use of nontoxic surrogate materials.

Section 9. Physical and chemical properties

Appearance: Liquid / Colorless.
Boiling point: Not available.
Odour: Not available.
Evaporation rate Not available. **Melting Point:** Not available.
Reactivity in Water Not available. **Vapour density:** Not available.
Percentage Volatile by volume: Not available.
Vapour pressure Not available.
Other information Not available **Density of solution**: 1.07 g/ml at room temperature.

Section 10. Stability and Reactivity

Condition to avoid: Avoid exposure to extreme heat, light and moisture.
Stable: Stable under recommended storage condition.
Decomposition products: No data available
Incompatibilities: Oxidizers, acids, and bases.
Hazardous Reaction: No data available

Section 11. Toxicological information

General: Handling of formulated product as per directions given in information leaflet is not expected to cause any toxicological affects. The data pertains to the ingredient in formulations.
Target organ: No data available.

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Section 12. Ecological information

Do not allow product to enter drinking water supplies, waste water or soil. Dispose the waste in accordance with all applicable Federal, State and local laws.

Section 13. Disposal Consideration

The product is not hazardous when shipping via air (IATA), ground (DOT),or sea(IMDG).

Section 14. Transport Information

FDA has approved NDA product under the brand name of AMMONUL with application Number: 020645 on February 17, 2005.

Section 15. Regulatory Information

Revision No.: New addition

References:

* Dippy, J. F. J.; Hughes, S. R. C.; Rozanski, A. (1959). "The dissociation constants of some symmetrically disubstituted succinic acids". *Journal of the Chemical Society* **1959**: 2492–2498

** Harris, Daniel (2010). *Quantitative Chemical Analysis* (8 ed.). New York: W. H. Freeman and Company. pp. AP12.

The information contained herein is based on the state of our knowledge. It characterizes the product with regard to the appropriate safety precautions. It does not represent a guarantee of the properties of the product.