

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-060**

**PHARMACOLOGY REVIEW**



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

## PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 20-645  
SERIAL NUMBER: 000  
DATE RECEIVED BY CENTER: 8/9/04  
PRODUCT: Ammonul  
INTENDED CLINICAL POPULATION: treatment of acute hyperammonemia  
SPONSOR: Ucyclid Pharma  
DOCUMENTS REVIEWED: Electronic  
REVIEW DIVISION: Division of Metabolic & Endocrine Drug Products  
(HFD-510)  
PHARM/TOX REVIEWER/ SUPERVISOR: Karen Davis-Bruno  
DIVISION DIRECTOR: David Orloff  
PROJECT MANAGER: Patricia Madara

Date of review submission to Division File System (DFS): 12/8/04

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## **EXECUTIVE SUMMARY**

### **I. Recommendations**

- A. Recommendation on approvability: Pharmacology/Toxicology recommends approval of this application based on the extensive clinical and nonclinical experience with 10% sodium benzoate/10% sodium phenylacetate.
- B. Recommendation for nonclinical studies: none
- C. Recommendations on labeling: Since this application is designated as a 505(b)2 submission, labeling is based on the reference product; Ucephan NDA 19-530, approved in 1987. Two minor changes for clarification are recommended.
  - 1) In the Precautions section; Neurotoxicity of Phenylacetate; Paragraph 2, after sentence 2 should read: **Pregnant rats were given phenylacetate at 3.5 umol/g/day SC from gestation day 7 through normal delivery.** Prenatal exposure of rat pups to phenylacetate produced lesions in layer 5 cortical pyramidal cells; dendritic spines were longer and thinner than normal and reduced in number [12].
  - 2) In the Carcinogenesis, Mutagenesis, Impairment of Fertility section the last sentence should read: **Results indicate that sodium benzoate is not mutagenic or carcinogenic, and does not impair fertility.**

### **II. Summary of nonclinical findings**

- A. Brief overview of nonclinical findings:

Limited nonclinical data has been provided by reference to published literature. However over twenty years clinical experience with this therapy in a wide variety of urea cycle disorders provides evidence of safety. The active drug substances (10% NaPA, 10% NaBZ) were previously approved for market as a drug product; Ucephan an oral solution used as an adjunct therapy to prevent and treat hyperammonemia with urea cycle enzymopathies (NDA 19-530; AP 12/23/87). Tablet and powder formulations of Buphenyl (sodium phenylbutyrate) the prodrug of sodium phenylacetate were approved for adjunctive therapy of patients with CPS, OTC and ASD urea cycle disorders (NDA 20-572; 5/13/96 tablet and NDA 20-573 4/30/96 powder).
- B. Pharmacologic activity: Sodium phenylacetate and sodium benzoate are nitrogen scavengers; binding waste nitrogen for urinary excretion. These components provide an alternative pathway for nitrogen disposal in cases where defects prevent the conversion of waste nitrogen into urea leading to accumulation of ammonia in an improperly functioning urea cycle. Two moles of nitrogen are removed per mole of phenylacetate when it is

conjugated with glutamine and one mole of nitrogen is removed per mole of benzoate when it is conjugated with glycine. The nitrogen scavenging effects occur via two separate reactions; the phenylacetate reaction is catalyzed by acetyl CoA:glutamine acyltransferase and glycine N-acyltransferase for benzoate. Each of these reactions has different kinetics with benzoate acting quickly and phenylacetate having a sustained effect. Since each compound has an independent, saturable elimination pathway the co-administration allows lower doses of each scavenger to be administered thus decreasing the toxicity. Phenylacetate reduces the levels of glutamine which may mediate some of the toxic effects of ammonia.

- C. Nonclinical safety issues relevant to clinical use: Phenylacetate given subcutaneously to neonatal rats 190-474 mg/kg (1200 mg/M<sup>2</sup>) is associated with loss, decreased proliferation and myelin in CNS neurons. Cerebral synapse production is retarded and reduced numbers of functioning nerve terminals in the cerebrum occurs resulting in impaired brain growth. Clinical dosing differs according to age/weight. The maximum clinical dose in children less than 20 kg is ~2.5 ml/kg which corresponds to a phenylacetate exposure of 625 mg/M<sup>2</sup> based on the clinical formulation of 100 mg/ml. Thus the neonatal rat study provides a 2-fold safety margin compared to the maximum clinical exposure in young children. However hyperammonemia can itself cause irreversible neurotoxicity leading to mortality, and Ammonul represents a therapeutic intervention to treat this condition in cases of congenital urea cycle disorders.
- Information available on Toxline suggests that low birthweight infants with immature livers may not be capable of metabolizing benzoate and hippurate. In vitro studies suggest that benzoate competes for bilirubin binding sites on albumin and should be used with caution in those with neonatal hyperbilirubinemia

## 2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

### 2.6.1 INTRODUCTION AND DRUG HISTORY

NDA 20-645

Review number: 1

Sequence number/date/type of submission: 000, 8/9/04

Information to sponsor: Yes (X) No ( )

Sponsor and/or agent: Ucyclid Pharma; Scottsdale, Arizona

Manufacturer for drug substance: sodium phenylacetate, \_\_\_\_\_  
\_\_\_\_\_ and sodium benzoate \_\_\_\_\_

Manufacturer for drug product: Chesapeake Biological Laboratories

Reviewer name: Davis-Bruno

Division name: Metabolic & Endocrine

HFD #: 510

Review completion date: 12/8/04

#### Drug:

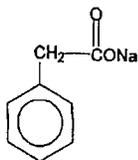
Trade name: Ammonul

Generic name: 10% sodium phenylacetate (NaPA) + 10% sodium benzoate (NaBZ)

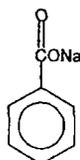
CAS registry number: 114-70-5 sodium phenylacetate; 532-32-1 sodium benzoate

Molecular Formula/ Molecular Weight: Sodium phenylacetate has a molecular weight of 158.13 and the molecular formula  $C_8H_7NaO_2$ . Sodium benzoate has a molecular weight of 144.11 and the molecular formula  $C_7H_5NaO_2$ .

Structure:



Sodium Phenylacetate



Sodium Benzoate

Relevant INDs/NDAs/DMFs: IND 17,123 ammonul (1986); \_\_\_\_\_  
\_\_\_\_\_ HFD-180; NDA 19-530 Ucephan AP 1987; NDA 20-573 (powder) & NDA 20-572 (tablets) Biphenyl (sodium phenylbutyrate) AP 1996

Drug class: nitrogen scavengers

Intended clinical population: adjunctive treatment of acute hyperammonemia and associated encephalopathies in patients with urea cycle enzyme deficiencies. Ammonul is not intended to replace dietary protein restriction, oral ammonia-scavenging drugs

(Buphenyl), amino acid supplements or dialysis but is intended for use in combination with these supportive therapies as needed.

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**Clinical formulation:** 100 mg sodium phenylacetate and 100 mg sodium benzoate per ml of water for injection; trace sodium hydroxide or HCl is present to adjust the pH. Ammonul must be diluted with sterile dextrose injection 10% before administration.

Generally 2.5 ml/kg Ammonul is used in children <20 kg however administration of concurrent arginine HCl dosing depends on the urea cycle disorder suspected and degree of encephalopathy. Arginine supplementation drives functional parts of the urea cycle. Similar concentrations of Ammonul are used in the maintenance dosing of children <20 kg. In adults or children >20 kg the loading and maintenance dose of 55 ml/M<sup>2</sup> Ammonul is used. Since administration of sodium phenylacetate and sodium benzoate circumvent the urea cycle they reduce elevated ammonia levels cause by enzyme deficiencies anywhere in the urea cycle therefore the same IV dose may be used for all urea cycle disorders.

**Route of administration:** intravenous bolus loading dose followed by IV infusion maintenance dose based on body weight for children or body surface area for adults.

**Disclaimer:** Tabular and graphical information are constructed by the reviewer unless cited otherwise.

**Data reliance :** Any information or data necessary for approval of NDA 20-645 that Ucylyd does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Ucylyd does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 20-645.

**Studies reviewed within this submission:** none submitted

**Studies not reviewed within this submission:** N/A

## 2.6.2 PHARMACOLOGY

### 2.6.2.1 Brief summary

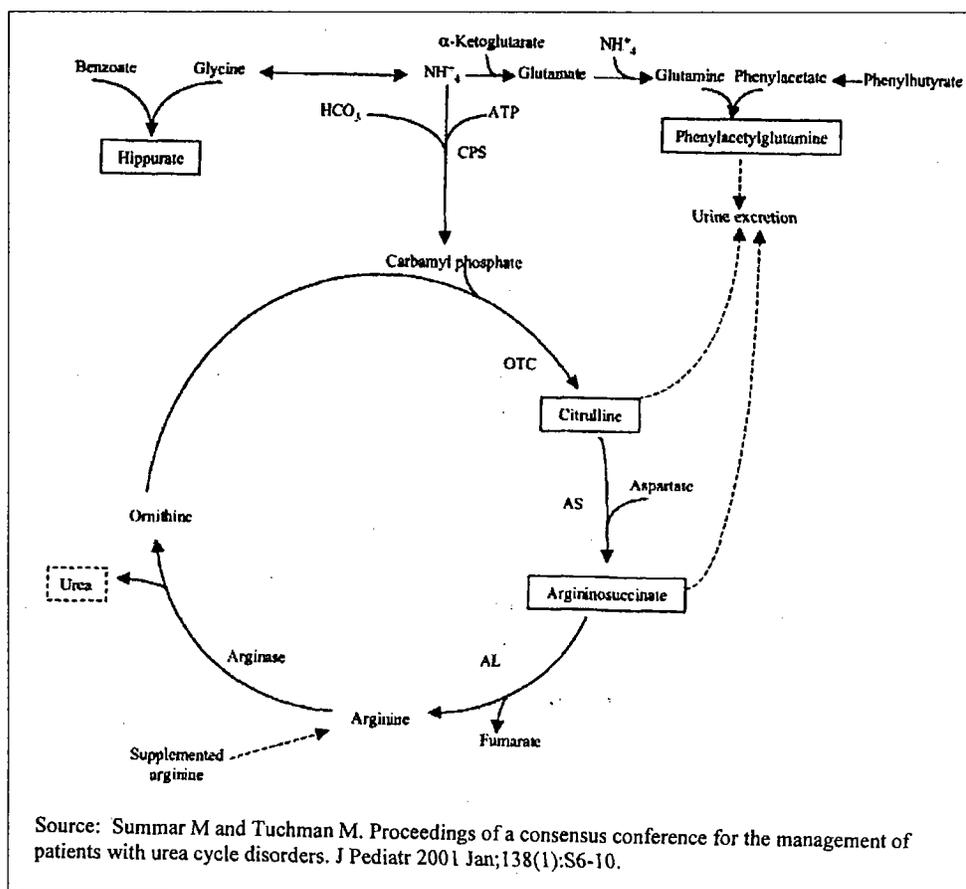
Loo et al. developed two animal models of phenylketonuria (PKU) using phenylacetate. In the first model rat pups were administered PA repeatedly. In the second model, pregnant female rats were given PA during gestation. The investigators claim that pups obtained from either model exhibit the biochemical, behavioral and morphological features of clinical PKU. The elevated phenylacetic acid in the brain derived from the

phenylalanine is the primary cause of brain dysfunction in PKU. Subsequent studies by this group attempted to elucidate the mechanism of PA induced neurotoxicity. One postulated mechanism is via a metabolic intermediate of PA; phenylacetyl-CoA which 1) decreases the availability of acetyl CoA and 2) in vitro is a potent inhibitor of choline acetyltransferase. Studies in rat demonstrating that postnatal exposure to PA significantly inhibits the utilization of acetyl CoA in fatty acid and sterol synthesis in vivo supports this. Although this model is useful in establishing induction of a PKU-like brain disorder, metabolites of phenylalanine including phenylacetate (PA) do not occur in human brain at levels sufficiently high enough to disturb metabolic and chemical relationships described in animal models. Radiolabeled PA (1.5  $\mu$ M/g) readily distributes to the brain of 1-7 day old rat pups but does not cross in older rats. Similar studies have been demonstrated in cats. Only when high concentrations of PA (>200 mg/min/10 min) was given at high continuous IV infusions was it measurable (radioactive tracer) in feline CSF.

#### 2.6.2.2 Primary pharmacodynamics

Mechanism of action: Sodium phenylacetate and sodium benzoate are nitrogen scavengers; binding waste nitrogen for urinary excretion. These components provide an alternative pathway for nitrogen disposal in cases where defects prevent the conversion of waste nitrogen into urea leading to accumulation of ammonia in an improperly functioning urea cycle. Therapeutic strategies are aimed at reducing the need for ureagenesis and provide a pathway for excretion of waste nitrogen by alternate means; substitutes for urea. Normally nitrogen is excreted in urine via the urea cycle completed in the liver. Waste nitrogen in the form of ammonia and other metabolites accumulate in patients with urea cycle or hepatic dysfunction leading to toxic effects particularly in the CNS. Progressive hyperammonemia results in cerebral edema, coma and death.

Appears This Way  
On Original



**Drug activity related to proposed indication:** Two moles of nitrogen are removed per mole of phenylacetate when it is conjugated with glutamine and one mole of nitrogen is removed per mole of benzoate when it is conjugated with glycine. The nitrogen scavenging effects occur via two separate reactions; the phenylacetate reaction is catalyzed by acetyl CoA:glutamine acyltransferase and glycine N-acyltransferase for benzoate. Each of these reactions have different kinetics with benzoate acting quickly and phenylacetate having a sustained effect. Since each compound has an independent, saturable elimination pathway the co-administration allows lower doses of each scavenger to be administered thus decreasing the toxicity. Phenylacetate reduces the levels of glutamine which may mediate some of the toxic effects of ammonia.

Urea cycle disorders are characterized by the complete or partial absence of one of the following urea cycle enzymes: carbamoylphosphate synthase (CPS), ornithine transcarbamylase (OTC), argininosuccinic acid synthetase (ASD), or argininosuccinic acid lyase (ASL) or arginase deficiency (ARD).

In higher primates, phenylacetate is conjugated with glutamine to form phenylacetylglutamine (PAG) which occurs rapidly in the liver and kidney. The reaction is catalyzed by fatty acyl CoA ligase and phenylacetyl coA:glutamine acetyltransferase with an acyl coA intermediate. In a second pathway, phenylacetate is activated by ATP

to yield phenylacetyl AMP which reacts with CoA-SH to form phenylacetyl coA which is then acylated with glutamine to form PAG.

Sodium benzoate is a food preservative which is rapidly absorbed, conjugated to glycine and excreted as hippurate. Hippurate substitutes for urea and ammonia as a waste nitrogen product.

#### **2.6.2.3 Secondary pharmacodynamics**

Phenylacetate (PA) has a number of effects associated with cancer, cystic fibrosis, sickle cell anemia and thalassemia. PA inhibits proliferation of prostate cancer cell lines and induces reversion to a nonmalignant phenotype. Anti-tumor activity may include reduction of circulating glutamine (main tumor cell energy source), activation of human PPAR, and inhibition of histone deacetylase activity. Histone deacetylases are involved cell transcription, cell cycle progression, gene silencing, cell differentiation, DNA replication and genotoxic responses. Other anti-tumor activities include:

- decreased myc oncogene expression, growth inhibition, promoted differentiation of leukemia cell line and mesenchymal cultures;
- promotion of neuroblastoma cell differentiation and growth inhibition when combined with retinoic acid;
- growth inhibition of rhabdomyosarcoma cells, K562 leukemia cells;
- inhibited proliferation and stimulated differentiation and production of fetal hemoglobin;
- inhibition of glioblastoma cell line growth
- reduced proliferation and increased fetal hemoglobin levels in erythroid precursor cells from normal donors and patients with sickle cell anemia or thalassemia.

Anti-tumor effects of PA have also been seen in animals. Rats with cerebral gliosarcomas received phenylacetate by continuous subcutaneous infusion with IP bolus dosing had extended survival. Morphology indicated that cell differentiation was induced.

In vitro activities for PA include:

- inhibition of mevalonic acid pathways for lipid, sterol and polyprenol synthesis
- inhibition of high affinity GABA uptake
- inhibition of Na/K ATPase
- inhibition of neuronal enzymes: choline acetyltransferase, DOPA decarboxylase, glutamic acid decarboxylase and 5-HT (serotonin) decarboxylase.

#### **2.6.2.4 Safety pharmacology**

**2.6.2.5 Pharmacodynamic drug interactions**

Because of structural similarities between benzoate and salicylates, exacerbation of peptic ulcer, mild hyperventilation and mild respiratory alkalosis may develop.

**2.6.3 PHARMACOLOGY TABULATED SUMMARY****2.6.4 PHARMACOKINETICS/TOXICOKINETICS****2.6.4.1 Brief summary****2.6.4.2 Methods of Analysis****2.6.4.3 Absorption**

Sodium benzoate is rapidly absorbed by mammals.

**2.6.4.4 Distribution :** (from Toxline) In rat, PA readily penetrates brain, eyes, heart, kidneys and liver. One hour post SC injection, in rats 1-65 days old the concentrations in plasma:tissue were approximately 1:1 in the above tissues except for brain which was higher. The blood-brain ratio changed from 1:1 in the 1-7 day old rat to the adult ration of 2:1 at 21 days of age.

**2.6.4.5 Metabolism:** Hippuric acid is the major metabolite of sodium benzoate and is excreted in urine (Toxline). Benzoate is conjugated to glycine to produce hippuric acid. Any remaining benzoate not converted to hippuric acid is effectively detoxified by conjugation with glucuronic acid and excreted as benzoyl glucuronide. This present an effective detoxification pathway whereby appreciable accumulation of benzoate is not observed.

In humans the primary route of phenylacetate metabolism is conjugation with glutamine via acetylation to form phenylacetylglutamine which is excreted from the kidneys via glomerular filtration and tubular secretion. This excretion pathway occurs in other species in addition to conjugation with glucine to yield phenylacetylglucine (phenylaceturic acid). Phenylacetate can be hydrolyzed by esterases (arylesterase in liver and plasma, carboxylesterase in liver microsomes/cytosol).

**2.6.4.6 Excretion**

In humans phenylacetate can be hydrolyzed by esterases in liver microsomes, cytosol and plasma. In all other species phenylacetate is excreted predominately as a glycine conjugate; phenylglycine (phenylaceturic acid).

Sodium benzoate is rapidly absorbed, conjugated to glycine and rapidly excreted in urine (>75% within 6 h) as hippurate. There is no accumulation of benzoate in the body.

When given in quantities >5 g some sodium benzoate is excreted as benzoyl glucuronide.

**2.6.4.7 Pharmacokinetic drug interactions :** Hypernatremia is possible in patients with diminished renal function (from Toxline). Antibiotics such as penicillin may compete with conjugated products of sodium benzoate and sodium phenylacetate for active

secretion by the renal tubules. Probenecid may inhibit renal transport and hence excretion of NaPA and NaPA.

#### **2.6.4.8 Other Pharmacokinetic Studies (Human PK):**

Protocol 951603 administered IV NaPA/NaBz in 90 minutes loading infusions and 24-h sustaining infusions of 5.5 g/m<sup>2</sup>. Severe emesis occurred in 3 healthy volunteers resulting in a reduction of dose to 3.75 g/m<sup>2</sup>. Following the priming dose, NaPA demonstrated nonlinear kinetics with a T<sub>max</sub>=1.7, C<sub>max</sub>=302.6±62 µg/ml and 411±29.9 µg/ml for high and low priming doses respectively. Clearance decreased with increased dose. Sodium benzoate also showed saturation of elimination with decreased clearance with increased dose. Similarly for NaBZ the C<sub>max</sub>=258.4±38.6 µg/ml at 1.5 h for the low dose and 416.7±34.6 µg/ml at 1.7 h for the high dose. Hippurate was detected at 15 minutes post dose and peaked 2.5-5 h. Phenylacetylglutamine (PAG) was detected at 0.75-2 h and peaked at 7.9 h for the low dose and continued to increase for the high dose. In the infusion phase of dosing following the priming dose NaPA and NaBZ peaked at or near the end of the priming dose. In the higher dose group T<sub>max</sub> of 7.2±5 h and the plateau duration of 9 h were higher and more prolonged than with the lower dose. No marked gender differences were observed.

**2.6.4.9 Discussion and Conclusions:** Toxline suggests that low birthweight infants with immature livers may not be capable of metabolizing benzoate and hippurate. In vitro studies suggest that benzoate competes for bilirubin binding sites on albumin and should be used with caution in those with neonatal hyperbilirubinemia.

#### **2.6.4.10 Tables and figures to include comparative TK summary**

### **2.6.5 PHARMACOKINETICS TABULATED SUMMARY**

### **2.6.6 TOXICOLOGY**

#### **2.6.6.1 Overall toxicology summary**

General toxicology: Subcutaneous phenylacetate at 190-474 mg/kg in rats decreases proliferation and increase loss of CNS neurons and reduces CNS myelin. Cerebral synapse production is retarded and a reduced number of functioning nerve terminals in the cerebrum occurs resulting in impaired brain growth.

A published report indicates that the oral LD<sub>50</sub> =2000mg/kg for sodium benzoate in the rat, rabbit and dog.

The following LD<sub>50</sub> thresholds for oral Ucephan® (an oral product of similar composition) are available (Summary Basis of Approval, 1987).

**Table 3.5-1. LD<sub>50</sub> Values for Ucephan® (Oral sodium phenylacetate [NaPA]/NaBZ)**

	Oral LD <sub>50</sub> (g/kg)	Intravenous LD <sub>50</sub> (g/kg)
Mice (males)	3.97	2.83
Mice (females)	3.64	3.00
Rats (males)	3.15	2.57
Rats (females)	2.86	2.86

Also, the maker of Ucephan® reported “no effect” on body weight, food consumption, serum chemistry, or hematology, and organ weights and histopathology were reported “good,” following 28 days of oral administration in rats (0.5 to 1 g/kg).

#### 2.6.6.2 Single-dose toxicity

The oral LD<sub>50</sub> for sodium benzoate in rat is 2100-4070 mg/kg. The oral LD<sub>50</sub> for sodium benzoate in rabbit and dog is 2000 mg/kg.

#### 2.6.6.3 Repeat-dose toxicity

Sodium phenylacetate (NaPA) has been studied in patients with refractory solid tumors given twice daily bolus infusions of 150 mg/kg for 14 days resulted in 2 episodes of Grade 3 neurotoxicity consisting of somnolence and hearing impairment. Cardiac events were observed in patients with preexisting cardiac disease and were presumed related to the sodium content. At 125 mg/kg an episode of somnolence was reported. Other AEs reported: fatigue, headache, dizziness, distortion/perversion of taste sensation, edema (foot), nausea, emesis and rash. Thus evidence in support of a relationship between CNS toxicity and PA plasma concentrations following continuous infusion was established in addition to evidence suggestive that PA plasma concentrations decreased with time in some patients, suggesting auto-induction of metabolism.

(Toxline) Single oral doses of 6 g sodium benzoate are tolerated in adults, although 1-1.5 g may cause vomiting. The maximum recommended dose in children is 500 mg/kg/day although toxicity has been seen with 200 mg/kg/day. Toxic effects are noted with plasma levels >80 mg/dL. Sodium benzoate is added directly to food and is considered GRAS with a current maximum level of 1% (Toxline). Sodium benzoate is used as an antimicrobial agent in food.

#### 2.6.6.4 Genetic toxicology

**2.6.6.5 Carcinogenicity:** No evidence of carcinogenicity was found in Fischer 344 rats given sodium benzoate at 1 or 2% in the diet for 18-24 months and no adverse clinical signs attributable to sodium benzoate were seen. Similarly lifetime administration of 2% sodium benzoate to albino Swiss mice was not tumorigenic.

#### 2.6.6.6 Reproductive and developmental toxicology:

Phenylacetate at 0.75-3.5 µmol/g/day for 20 days in rat pups obtained by continuous infusion of pregnant rats to achieve plasma levels of 0.25-0.45 µmol/ml resulted in biochemical, behavioral and morphologic features of clinical PKU (phenylketonuria) thus serving as an experimental model of PKU.

Prenatal exposure of rat pups to phenylacetate produces lesions in layer 5 cortical pyramidal cells and produces dendritic spines that are longer and thinner than normal and reduced in numbers.

#### **2.6.6.7 Local tolerance**

#### **2.6.6.8 Special toxicology studies**

In vitro sodium benzoate impairs lymphocyte mitogenesis. Sodium benzoate decreases chemiluminescence, superoxide anion and lysozyme release by PMN leukocytes stimulated with *Staphylococcus aureus* and impairs the ability of PMN leukocytes to kill *S aureus*. Thus sodium benzoate may have immunologic effects although it is commonly used as a food preservative. There have been reports of urticaria due to sodium benzoate exposures in manufacturing plants. Studies with rat mast cells indicated that sodium benzoate does not cause degranulation or histamine release thus the human response is thought to be non-immunologic.

#### **2.6.6.9 Discussion and Conclusions**

#### **2.6.6.10 Tables and Figures**

### **2.6.7 TOXICOLOGY TABULATED SUMMARY**

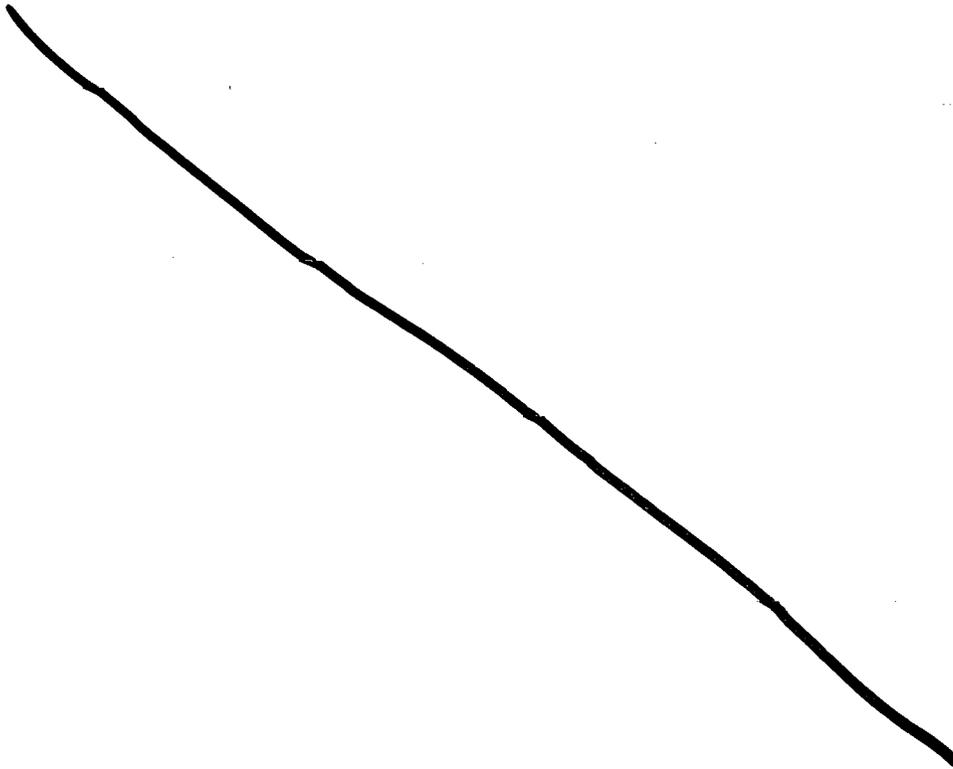
#### **OVERALL CONCLUSIONS AND RECOMMENDATIONS**

Conclusions: There is 22 years of clinical open label experience with this therapy in a wide variety of urea cycle disorders. The active drug substance (10% NaPA, 10% NaBZ) were previously approved for market as a drug product; Ucephan an oral solution used as an adjunct therapy to prevent and treat hyperammonemia with urea cycle enzymopathies (NDA 19-530; AP 12/23/87). Tablet and powder formulations of Buphenyl (sodium phenylbutyrate) the prodrug of sodium phenylacetate were approved for adjunctive therapy of patients with CPS, OTC and ASD urea cycle disorders (NDA 20-572; 5/13/96 tablet and NDA 20-573 4/30/96 powder)

Recommendations: approval

Suggested labeling: The approved Ucephan NDA 19-530 label forms the basis of the sponsor's proposed label. Two comments are recommended for clarification.

The sponsor's proposed labeling related to nonclinical data:



**Reviewer's proposed changes to labeling:**

- 3) In the Precautions section; Neurotoxicity of Phenylacetate; Paragraph 2, after sentence 2 should read: **Pregnant rats were given phenylacetate at 3.5  $\mu$ mol/g/day SC from gestation day 7 through normal delivery.** Prenatal exposure of rat pups to phenylacetate produced lesions in layer 5 cortical pyramidal cells; dendritic spines were longer and thinner than normal and reduced in number [12].
- 4) In the Carcinogenesis, Mutagenesis, Impairment of Fertility section the last sentence should read: **Results indicate that sodium benzoate is not mutagenic or carcinogenic, and does not impair fertility.**

APPENDIX/ATTACHMENTS N/A

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this page is the manifestation of the electronic signature.**  
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/s/

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Karen Davis-Bruno  
12/8/04 03:52:24 PM  
PHARMACOLOGIST  
approval with minor labelling changes