CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-645

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	20,645	Brand Name	Ammonul®
OCPB Division (I, II, III)	DPE-II	Generic Name	(Sodium phenylacetate/sodium benzoate 10%) injection
Medical Division	Metabolic and Endocrine Drug Products	Drug Class	Nutrients
OCPB Reviewer	Jaya bharathi Vaidyanathan, Ph.D.	Indication(s)	Treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle
OCPB Team Leader	Hae-Young Ahn, Ph.D.	Dosage Form	100 mg/ml sodium phenylacetate/ 100 mg/ml sodium benzoate Injection solution
		Dosing Regimen	Neonates; infants; young children: 250 mg/kg loading dose over 2 hr and 250 mg/kg maintenance dose over 24 hr. Older children; Adults: 5.5 g/m^2 loading dose over 2 hr and 5.5 g/m^2 maintenance dose over 24 hr.
Date of Submission	8/9/04	Route of Administration	Intravenous
Estimated Due Date of OCPB Review		Sponsor	Medicis Pharmaceutical Corporation
PDUFA Due Date	2/10/05	Priority Classification	P
Division Due Date	2/1/05	Submission	Electronic

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	1	

multiple dose:	X	1	1	
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		2	2	

Filability and QBR comments				
	"X" if yes	**Comments**		
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?				
QBR questions (key issues to be considered)	**What are the pharmacokinetics parameters of sodium phenylacetate and sodium benzoate after iv administration?**			
Other comments or information not included above				
Primary reviewer Signature and Date	**Jaya bharathi Vaidyanathan**			
Secondary reviewer Signature and Date	**Hae-Young Ahn**			

On August 9, 2004, Medicis Pharmaceutical Corporation submitted NDA 20-645 for Ammonul® (sodium phenylacetate/sodium benzoate 10%) injection. This is a resubmission and was refused to file previously on April 28, 1998 and October 5, 2000. Ammonul® was granted orphan drug status for the treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle.

There are 2 PK studies submitted in support of this application:

1) Study 951603: Pharmacokinetic study of sodium phenylacetate/sodium benzoate administered as IV infusions in healthy adult volunteers.
2) Study 973600: Pharmacokinetic study of sodium phenylacetate/sodium benzoate administered as IV infusions (1 gm/m^2, 2 gm/m^2, 4 gm/m^2) in healthy adult male volunteers.

The pharmacokinetic results of Ammonul® are summarized as follows:

Study 951603: Subjects received a loading dose of either, 3.75 gm/m^2 or 5.5 gm/m^2 once followed by a 24 hr sustaining infusion. Drug and metabolite PK was followed. After the priming dose, sodium phenylacetate demonstrated nonlinear kinetics. Clearance decreased from 1.82 ± 0.35 to 0.89 ± 0.28 L/h/ m^2 with increased dose. Sodium benzoate also demonstrated saturable elimination with decreased clearance with increased dose. No marked gender differences were observed.

Study 973600: Subjects received escalating loading dose once. Sodium benzoate displayed nonlinear PK, with C_{max} increasing disproportionately with dose. Sodium phenylacetate

also had nonlinear PK. Hippurate was detected within 15 min while phenylacetylglutamine was detected at 0.5 to 1.5 hr. Both of these metabolites increased proportionally with dose.

PK information for Ammonul® has also been included from various references in the literature.

The clinical trial formulation is similar to the commercial batch.

Conclusions:

NDA 20-645 is fileable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jayabharathi Vaidyanathan
10/5/04 02:23:45 PM
PHARMACOLOGIST

Hae-Young Ahn
10/6/04 01:39:37 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-645	Submission Date(s): 8/9/04
Brand Name	Ammonul™
Generic Name	Sodium phenylacetate/ sodium benzoate injection
Reviewer	Jaya bharathi Vaidyanathan, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPEII
ORM Division	Division of Metabolic and Endocrine Drug Products
Sponsor	Medicis Pharmaceutical Corporation
Submission Type; Code	505 (b) (2); Priority
Relevant IND	17,123
Formulation; Strength(s)	IV injection; 10% solution
Indication	Treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle

Table of Contents

I. Executive Summary

Medicis submitted NDA 20-645 Ammonul™ (sodium phenylacetate/sodium benzoate 10%) for use as an adjunctive therapy for the treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle, and as a prophylactic therapy to prevent hyperammonemia in neonates diagnosed as having deficiencies of a urea cycle enzyme.

The current submission contains 2 studies under the Clinical Pharmacology and Biopharmaceutics section.

1) Study 951603: Pharmacokinetic study of sodium phenylacetate/sodium benzoate administered as IV infusions in healthy adult volunteers.
2) Study 973600: Pharmacokinetic study of sodium phenylacetate/sodium benzoate administered as IV infusions (1 gm/m^2, 2 gm/m^2, 4 gm/m^2) in healthy adult male volunteers.

In these studies plasma concentrations of benzoic acid, its metabolite hippurate, phenylacetate and its metabolite phenylacetylglutamine were measured. In study 951603, normal subjects were given 90 min loading infusions and 24-h sustaining infusions of 5.5 gm/m^2 sodium benzoate/sodium phenylacetate. This regimen caused severe emesis in the first 3 subjects and the next 17 subjects were given a reduced dose of 3.75 gm/m^2. After the loading dose, sodium benzoate demonstrated saturable elimination as evidenced by decreased clearance (5.19 L/hr/m^2 to 3.62 L/hr/m^2) with increase in dose. Phenylacetate also displayed non-linear kinetics. The clearance decreased from 1.82 L/hr/m^2 to 0.89 L/hr/m^2 with increased dose. The AUC_{last} was 737 μg.hr/ml with 3.75 gm/m^2 and 2473.2 μg.hr/ml after the 5.5 gm/m^2 infusion over 24 h for benzoic acid and for 3532.5 gm/m^2 and 8366.6 gm/m^2 phenylacetate respectively.

In the second study, # 973600 6 subjects were given loading infusions (1, 2, and 4 gm/m^2) only. Sodium benzoate displayed non-linear kinetics with C_{max} increasing disproportionately with dose (18.6, 82, and 231.8 μg/ml) and T_{max} of 1.5 h. Phenylacetate also showed similar kinetics with T_{max} of 1.5-1.7 h and C_{max} increasing with dose (72.7, 173.4, and 306.6 μg/ml). AUC for both metabolites hippurate and phenylacetylglutamine increased proportionately with dose.

No dose finding studies were conducted for Ammonul™ and pharmacokinetic-pharmacodynamic relationship was not explored.

A. Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 20-645 and finds the Clinical Pharmacology section of the NDA acceptable. Recommendation and labeling comments should be conveyed to sponsor as appropriate.

CPB briefing was held on 1/25/05 and the attendees were Hank Malinowski, John Hunt, Arzu Selen, Hae-Young Ahn, Bill Lubas, Pat Madara, and Jayabharathi Vaidyanathan.

B. Phase IV Commitments

None.

C. Summary of CPB Findings

The pharmacokinetic parameters of benzoic acid and phenylacetate were characterized in healthy subjects from two PK studies.

Study 951603:
Plasma concentrations time profiles were generated at two dose levels (3.75 and 5.5 gm/m^2) following a single loading dose (period 1) (90 min) and a loading dose followed by a maintenance dose infusion (period 2) over 24 h. Following the loading dose regimen both benzoic acid and phenylacetate demonstrated saturable elimination as evidenced by decreased clearance with increase in dose. The clearance decreased from 5.19 $L/hr/m^2$ to 3.62 $L/hr/m^2$ for benzoic acid and from 1.82 $L/hr/m^2$ to 0.89 $L/hr/m^2$ for phenylacetate following the administration of 3.75 gm/m^2 and 5.5 gm/m^2 dose respectively. There was a greater than dose-proportional increase in both AUC and C_{max} for benzoic acid and in AUC for phenylacetate. The metabolites, hippurate and phenylacetate AUCs increased proportionally with dose, while increase in C_{max} was less than dose proportional.

Study 973600:
Similar results were obtained for both parent compounds and metabolites in this 3-period escalating dose study (1, 2, and 4 gm/m^2). Benzoic acid AUC and C_{max} increased in a greater than dose proportional manner, while for phenylacetate there was a greater than dose proportional increase in AUC. The metabolites, hippurate and phenylacette AUC increased proportionally with dose.

II QBR

A. General Attributes

What is the regulatory background for Ammonul™?

Urea cycle disorders are rare inborn metabolic diseases characterized by partial or complete inactivity of one of several enzymes of urea cycle. Initially, patients were treated with benzoate as the only pharmacologic therapy, both oral and intravenous, and phenylacetate was subsequently coadministered. The use of the combination sodium phenylacetate/sodium benzoate (NaPA/NaBZ) for the treatment of urea cycle deficiencies was initiated under Investigational New Drug (IND 17,123). Since 1992 the combination product, sodium phenylacetate/sodium benzoate has been a FDA designated orphan drug

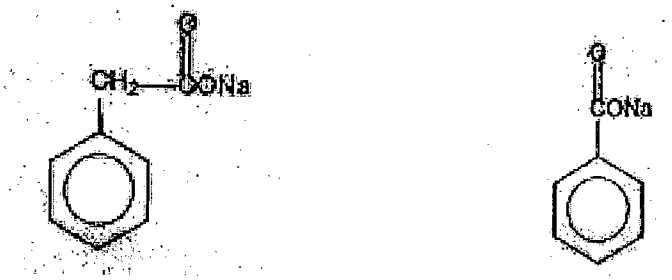
product. Initially, IND 17, 123 investigated the use of Ucephan® (oral NaPA/NaBZ) and Buphenyl (oral sodium phenylbutyrate, the prodrug of NaPA) as chronic drugs for urea cycle disorders. FDA had approved NDA 19-530, Ucephan®, in 1987 however it is currently discontinued. During the course of the study, the protocol was amended for the use of 10% NaPA/NaBZ IV injection for treatment. This NDA is a resubmission and was previously refused to file by the agency twice, once in 1998 and in 2000 due to multiple clinical deficiency issues.

What are the highlights of the physico-chemical properties of Ammonul™?

The aqueous injection formulation contains two active substances, sodium phenylacetate and sodium benzoate (Figure 1). Both are white crystalline powder and freely soluble in water and methanol.

Figure 1: Structure of the active ingredients in Ammonul™

Sodium phenylacetate **Sodium benzoate**

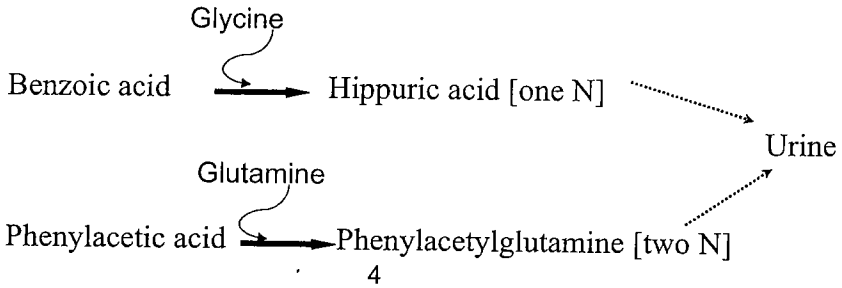


What is the indication and mechanism of action of Ammonul™?

Ammonul™ is indicated for use as an adjunctive therapy for the treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle, and as a prophylactic therapy to prevent hyperammonemia in neonates diagnosed as having deficiencies of a urea cycle enzyme.

Both phenylacetate and benzoate decrease plasma ammonia by producing alternative vehicles for waste nitrogen as phenylacetylglutamine and hippurate. Phenylacetate is a product of phenylalanine metabolism and is normally present in mammalian circulation at low concentrations. It conjugates to glutamine-associated nitrogen with a concomitant decrease in serum levels of ammonia. Benzoic acid conjugates to glycine with a decrease in ammonia levels (Figure 2).

Figure 2: Schematic diagram of mechanism of action of Ammonul™.



What is the proposed dosage and route of administration for Ammonul™?

Ammonul is administered intravenously as a 90 minute loading dose infusion followed by a 24 hour maintenance dose infusion. Ammonul must be diluted with sterile dextrose injection, 10% before administration. Intravenous arginine is an essential component of therapy for patients with carbamyl phosphate synthetase (CPS), ornithine transcarbmylase (OTC), argininosuccinate synthetase (AS), argininosuccinate lyase (AL) deficiency. The dilution and dosage of Ammonul is determined by weight for infants and young children and by body surface area for older children, adolescents and adults. The dosage information is summarized in Table 1.

Table 1: Dosage and administration for Ammonul

Patient Population	Components of Infusion Solution			Dosage Provided		
	Ammonul	Arginine HCl Injection, 10%	Dextrose Injection, 10%	Sodium Phenylacetate	Sodium Benzoate	Arginine HCl
Neonates:						
CPS and OTC Deficiency						
Loading Dose (over 1.5 – 2 h)	2.5 mL/kg	2.0 mL/kg	=25 mL/kg	250 mg/kg	250 mg/kg	200 mg/kg
Maintenance Dose (over 24 h)*	2.5 mL/kg	2.0 mL/kg	=25 mL/kg	250 mg/kg	250 mg/kg	200 mg/kg
AS and AL Deficiency						
Loading Dose (over 1.5 – 2 h)	2.5 mL/kg	6.0 mL/kg	=25 mL/kg	250 mg/kg	250 mg/kg	600 mg/kg
Maintenance Dose (over 24 h)*	2.5 mL/kg	6.0 mL/kg	=25 mL/kg	250 mg/kg	250 mg/kg	600 mg/kg
Infants and Young Children:						
CPS and OTC Deficiency						
Loading Dose (over 1.5 – 2 h)	2.5 mL/kg	2.0 mL/kg	=25 mL/kg	250 mg/kg	250 mg/kg	200 mg/kg
Maintenance Dose (over 24 h)*	2.5 mL/kg	2.0 mL/kg	=25 mL/kg	250 mg/kg	250 mg/kg	200 mg/kg
AS and AL Deficiency						
Loading Dose (over 1.5 – 2 h)	2.5 mL/kg	6.0 mL/kg	=25 mL/kg	250 mg/kg	250 mg/kg	600 mg/kg
Maintenance Dose (over 24 h)*	2.5 mL/kg	6.0 mL/kg	=25 mL/kg	250 mg/kg	250 mg/kg	600 mg/kg
Older Children and Adults:						
CPS and OTC Deficiency						
Loading Dose (over 1.5 – 2 h)	55 mL/m^2	2.0 mL/kg	=25 mL/kg	5.5 g/m^2	5.5 g/m^2	200 mg/kg
Maintenance Dose (over 24 h)*	55 mL/m^2	2.0 mL/kg	=25 mL/kg	5.5 g/m^2	5.5 g/m^2	200 mg/kg
AS and AL Deficiency						
Loading Dose (over 1.5 – 2 h)	55 mL/m^2	6.0 mL/kg	=25 mL/kg	5.5 g/m^2	5.5 g/m^2	600 mg/kg
Maintenance Dose (over 24 h)*	55 mL/m^2	6.0 mL/kg	=25 mL/kg	5.5 g/m^2	5.5 g/m^2	600 mg/kg

* Maintenance infusions may be continued at the same dose at the clinician's discretion.

B. General Clinical Pharmacology

What clinical pharmacology studies are submitted in this NDA?

The current submission contains 2 studies under the Clinical Pharmacology and Biopharmaceutics section.

- Study 951603: Pharmacokinetic study of sodium phenylacetate/sodium benzoate administered as IV infusions in healthy adult volunteers.
- Study 973600: Pharmacokinetic study of sodium phenylacetate/sodium benzoate administered as IV infusions (1 gm/m^2, 2 gm/m^2, 4 gm/m^2) in healthy adult male volunteers.

What are the major findings about exposure-response relationships?

No exposure-response studies for efficacy or safety have been submitted for this NDA. According to the reviewing medical officer Dr. Bill Lubas, there is no data indicating any kind of dose-response study in the clinical report submitted. Sponsor has stated that doses were developed from an empiric calculation which estimated nitrogen elimination needed to reduce elevated levels of ammonia and glutamine based on the molar replacement equivalent of pheylacetylglutamine and hippurate derived from 24-h infusion. The time required for the elevated ammonia levels to reduce to normal range takes about 6 h. Most of the patients receive Ammonul once and depending on their conditions either receives oral therapy or need to have dialysis.

The primary endpoint for efficacy was the survival status of the patients. Secondary endpoints for efficacy were neurological status at admission and discharge, change from baseline in blood ammonia levels and number and percentage of patients who received dialysis excluding neonatal rescue patients.

Does this drug prolong QT or QTc interval?

The effect of this drug on QT interval has not been determined by the sponsor. No information is available in the literature regarding the effect of sodium benzoate or sodium phenylacetate on QT interval.

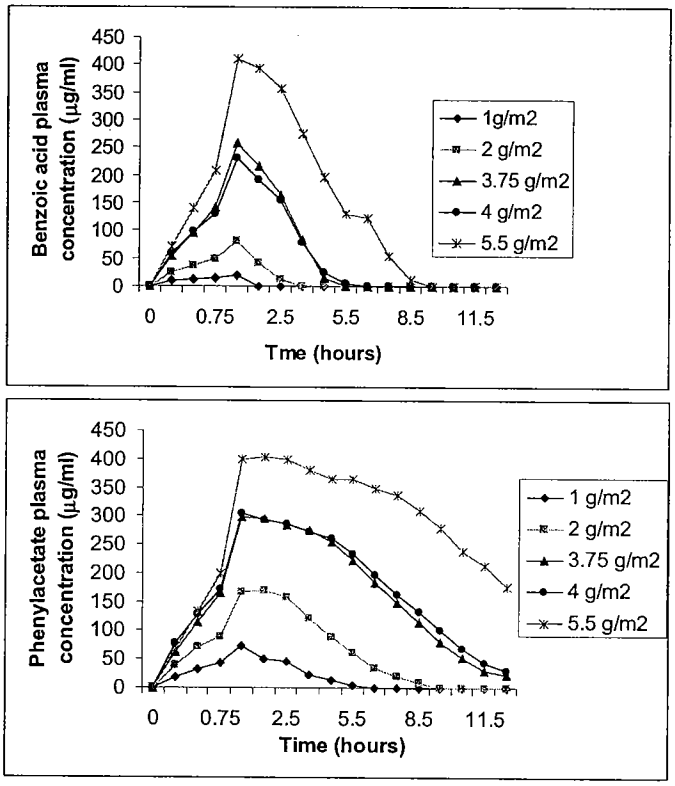
What are the characteristics of Ammonul™ pharmacokinetics?

The pharmacokinetics of Ammonul™ was characterized in healthy volunteers by the sponsor in two separate studies. Study 951603 was a two period study which included administration of a loading dose (90 min) of 3.75 and 5.5 g/m^2 in period 1 while period 2 consisted of administration of a loading dose (3.75 or 5.5 g/m^2) followed by a continuous infusion (3.75 or 5.5 g/m^2) over 25 hours. The second pharmacokinetic study 973600 was a crossover study with administration of 1, 2, and 4 g/m^2 as a loading dose over 90 min.

After loading dose only:

Figure 3 shows combined results of the plasma concentrations of benzoic acid and phenylacetate from the two PK studies. Plasma phenylacetate levels are higher than those of benzoic acid following each dose. There is a greater than dose proportional increase in AUC and C_{max} for benzoic acid and AUC for phenylacetate. There was a decrease in the clearance of both the compounds with increasing dose, indicating saturable elimination.

Figure 3: Mean plasma concentrations after different dose loading infusion over 1.5 hours for benzoic acid (top panel) and phenylacetate (bottom panel).



The associated pharmacokinetic parameters after administration of loading dose are shown in the following Tables, 2 and 3.

Table 2: Benzoic acid and phenylacetate PK parameters following NAPA/NABZ 3.75 g/m^2 and 5.5 g/m^2 x 1.5 h

Parameter	Benzoic Acid				Phenylacetate			
	N	3.75 g/m^2	N	5.5 g/m^2	N	3.75 g/m^2	N	5.5 g/m^2
AUClast(µg.hr/ml) Mean (SD)	17	564.6 (103.9)	3	1599.1 (463.1)	17	2040.6 (332.5)	3	3829.2 (516.6)
C_{max} (µg/ml) Mean (SD)	17	258.4 (38.6)	3	416.7 (34.6)	17	302.6 (42.0)	3	411 (29.9)
CL ($L/hr/m^2$) Mean (SD)	17	5.19 (2.23)	3	3.62 (1.24)	17	1.82 (0.35)	3	0.89 (0.28)
T_{max} (hr) Mean (SD)	17	1.5 (0)	3	1.7 (0.3)	17	1.7 (0.3)	3	1.7 (0.3)
Vd (L/m^2) Mean (SD)	17	5.09 (2.15)	3	6.63 (0.96)	17	7.2 (1.32)	3	12.43 (0.62)

Table 3: Benzoic acid and phenylacetate PK parameters following NAPA/NABZ priming infusion over 1.5 hours

Parameter	Benzoic Acid			Phenylacetate		
	1 g/m^2	2 g/m^2	4 g/m^2	1 g/m^2	2 g/m^2	4 g/m^2
AUClast(µg.hr/ml) Mean (SD)	20.3 (3.6)	114.9 (31.3)	562.8 (142.3)	175.6 (45.1)	713.8 (116.6)	2181.6 (249)
C_{max} (µg/ml) Mean (SD)	18.6 (4.1)	82.0 (18.4)	231.8 (25.5)	72.7(10.7)	173.4 (9.6)	306.5 (11.0)
T_{max} (hr) Mean (SD)	1.5 (0)	1.5 (0)	1.5 (0)	1.5 (0)	1.7 (0.3)	1.5 (0)

The metabolite pharmacokinetic parameters obtained following administration of loading dose over 90 min are summarized in Table 4. The hippurate was detectable in plasma for a longer time with the 5.5 g/m^2 dosing group than at the lower dose. The plasma concentration time profile for phenylacetylglutamine was very different than hippurate; with the lower dosing group there was no detectable plasma phenylacetyl glutamine till about 2 h and then it gradually increased. While at the higher dosing group, the concentration increased over the entire sampling period. At the highest dosing group, there was no decline of the phenylacetylglutamine concentrations and therefore the PK parameters could not be calculated. The T_{max} of both the metabolites increase with increase in dose.

Table 4: Hippurate and phenylacetylglutamine pharmacokinetic parameters after different dose loading infusion over 1.5 hours

Parameter	Hippurate					Phenylacetylglutamine				
	1 g/m^2	2 g/m^2	3.75 g/m^2	4 g/m^2	5.5 g/m^2	1 g/m^2	2 g/m^2	3.75 g/m^2	4 g/m^2	5.5 g/m^2
AUClast(µg.hr/ml) Mean (SD)	59.1 (13.7)	117.0 (37.6)	236.80 (49.49)	228.8 (48.1)	518.26 (45.73)	163.1 (26)	376 (60.3)	542.32 79.022	688.3 (52.2)	Not determined
C_{max} (µg/ml) Mean (SD)	33.2 (6.0)	48.6 (14)	62.41 (11.63)	57.4 (17.3)	77.47 (20.11)	43.4 (8.5)	66 (14.1)	74.18 11.011	91.4 (3.4)	
Tmax (hr) Mean (SD)	1.5 (0)	2.0 (0.3)	3.029 (0.514)	3.5 (0.6)	5.166 (0.577)	2.8 (0.5)	4.5 (0)	7.911 0.870	7.7 (1.6)	

The data from study # 973600 were fit into a one-compartment model with Michaelis-Menten elimination. The model parameters were determined by the sponsor as follows: Benzoic acid: $V_{max} = 94 \pm 21$ µg/h/L/m^2, $K_m = 14.5 \pm 3.1$ µg/ml and $V = 94 \pm 21$ L/m^2. Phenylacetate: $V_{max} = 34.7 \pm 4.1$ µg/h/L/m^2, $K_m = 36.0 \pm 9.2$ µg/ml and $V = 10.5 \pm 0.2$ L/m^2.

Comments:

The sponsor has not provided the details of how the data was fit to Michaelis-Menten one-compartment model. Individual plasma concentration time profiles for the 6 subjects show that there was wide range of concentrations for the middle dose as compared to the lower and highest doses and therefore suggests that this dose might give a better estimate of K_m and V_{max}. The plasma concentration versus time data for both phenylacetate and benzoate after administration of 2 g/m^2 dose was analyzed using Michaelis-Menten one-compartment model in WinNonlin.

The mean of the model parameters (N=6) were as follows:
Benzoic acid: $K_m = 19.26$ µg/ml, $V_{max} = 117.12$ mg/hr/l/m^2 and $V = 10.17$ L/m^2.
Phenylacetate: $K_m = 23.09$ µg/ml, $V_{max} = 38.21$ mg/hr/l/m^2 and $V = 8.89$ L/m^2.

After loading dose followed by maintenance dose:

The pharmacokinetic parameters for benzoic acid and phenylacetate are provided in Table 5 after the administration of 3.75 g/m^2 and 5.5 g/m^2 loading and continuous infusion over 25.5 h. For benzoic acid the Tmax was similar for both dose groups (1.5 h). In contrast, for phenylacetate the peak concentration was 2 h for the low dose and much later for the higher dose group (7.2 h). For both benzoic acid and phenylacetate there was greater than dose proportional increase in exposure. Plasma benzoic acid levels continuously decline during the infusion period in both dose groups. The peak

phenylacetate concentration occurred later with the high dose and the duration of plateau during the infusion was much longer with the high dose. This phase was followed by a continuous decline in concentration.

Hippurate levels on the other hand increase above the benzoic acid concentration at around 5 h for the low infusion dose and 10.5 h for the high infusion dose groups. The Tmax for hippurate occurred at 3.4±1.0 h and 5.8±1.2 h respectively for the two groups. Phenylacetylglutamine Tmax was achieved at 8.8±1.7 h and 19.5±5.2 h in the low and high dose groups respectively.

Table 5: Benzoic acid and phenylacetate PK parameters following NAPA/NABZ 3.75 g/m^2 and 5.5 g/m^2 priming and continuous infusion over 25.5 hours

Parameter	Benzoic Acid				Phenylacetate			
	N	3.75 g/m^2	N	5.5 g/m^2	N	3.75 g/m^2	N	5.5 g/m^2
AUClast(μg.hr/ml) Mean (SD)	14	737 (129.7)	3	2473.2 (878.7)	14	3532.5 (685.5)	3	8366.6 (1062)
C_{max} (μg/ml) Mean (SD)	14	264 (36)	3	449.7 (159.8)	14	307.4(36.9)	3	465.4 (49.6)
T_{max} (hr) Mean (SD)	14	1.5 (0)	3	1.5 (0)	14	2.0 (1.1)	3	7.2 (5.0)

Comments:

The mean Tmax reported by the sponsor for phenylacetate after the 5.5 g/m^2 infusion was 7.2 h. Considering the loading dose infusion for 1.5 h followed by the continuous infusion over 25 h, this seems to be very delayed. There were 3 subjects in this group who had large differences in their individual Tmax which were 6.5, 12.5 and 2.5 h. The corresponding clearance for these 3 subjects was 0.0007, 0.0006, 0.0007 $L/hr/m^2$ respectively. The reviewer reanalyzed the data submitted by the sponsor and obtained similar results. No explanation has been given by the sponsor. Considering this large variability and the limited number of subjects no conclusions can be drawn on the time to maximum concentration following administration of 5.5 g/m^2 dose infusion for phenylacetate.

Is Ammonul™ pharmacokinetics in target population different from that in healthy?

Sponsor has not conducted any PK study in patients with hyperammonemia. There is some information of PK parameters of sodium benzoate in neonates with hyperammonemia (parenteral) compared to healthy adult volunteers (oral) in the literature. The benzoic acid PK was described using a first order, one compartment elimination model, and a one compartment model with Michaelis-Menten elimination. The results are summarized in Table 6

Table 6 Benzoic acid PK models

Population	Route and Dose	Model	Parameter	Reference
2 patients with hyperammonemia	Oral NABZ 130 and 150 mg/Kg	One-compartment with Michaelis-Menten elimination	Patient 1: Vmax = 152 µg/ml/hr Km = 65.7 µg/ml Patient 2: Vmax = 90 mg/ml/hr Km = 30 µg/ml	Oyanagi K et.al. J Pediatrics 1987; 110:634-636
6 healthy adults	Oral benzoic acid @ 3 doses (40, 80, 160 mg/Kg)	One-compartment with Michaelis-Menten elimination	Vmax = 101.9 µg/ml/hr Km = 10.5 µg/ml Cmax (for 3 doses) = 99.7, 202.8, 336.5 µg/ml	Kubota K et. al. Eur J Clin Pharmacol 1991; 41:363-368
4 neonates with hyperammonemia	IV NABZ 3.5 mM/kg/day divided Q6h	Assumed first order, one compartment elimination model	Large interpatient variability Vd= 0.14 ±0.07 L/kg T1/2 = 2.8 ±3.1 hr CL = 1.0±0.61 ml/kg/min	Green TP et. al. J Pediatrics 1983: 102: 785.

What is known about the metabolism of Ammonul™?

The metabolism of phenylacetate and benzoate has been documented in literature since early 1900s. Numerous articles have reported the metabolism after oral administration and are summarized in Table 7. The major metabolites eliminated in urine after the administration of sodium phenylacetate and sodium benzoate are phenylglutamine and hippurate (Figure 3) respectively.

In humans, phenylacetate undergoes hepatic conjugation with glutamine by phenylacetyl coenzyme A:glutamine acyltransferase, which yields phenylacetylglutamine, the primary metabolite. Similarly, benzoic acid also undergoes hepatic conjugation with glycine in the presence of acetylcoenzyme A to form hippurate. Both phenylacetylglutamine and hippurate are excreted in the urine.

Figure 3: Structure of the metabolites of sodium phenylacetate and sodium benzoate

Phenylacetylglutamine **Hippurate**

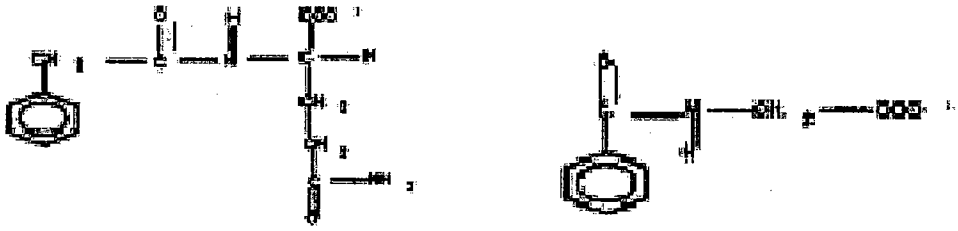


Table 7: Summary of metabolism of sodium phenylacetate and sodium benzoate (literature)

Drug	Oral Dose	Metabolism	Reference
Sodium benzoate	6-10 g	85-90% of dose as hippuric acid in urine within 5-6 h.	Lewis, HB. J Biol. Chem 1914; 27:225-231
Sodium benzoate	3 g	89-93% of dose as hippuric acid in urine within 6h.	Shiple GJ, Sherwin CP. J Am Chem Soc 1922; 618-624
Sodium phenylacetate	3.3 g	90% of dose as phenylacetylglutamine in urine within 12 h.	Shiple GJ, Sherwin CP. J Am Chem Soc 1922; 618-624
Sodium phenylacetate	Up to 10 g	95% of dose as phenylacetylglutamine in urine within 12 h and 5% as glucuronic acid conjugate.	Ambrose AM et al. J Biol Chem 1933; 101:669-675

C. Intrinsic Factors

What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, renal or hepatic impairment) influence exposure and response?

Sponsor has not evaluated the effect of intrinsic factors such as age, race, weight, height, disease, genetic polymorphism, pregnancy, gender, renal impairment or hepatic impairment on the pharmacokinetics of Ammonul™ in thorough PK studies. However, data available from the literature in infants and children is available. This data obtained from 7 children (age 3 months to 26 months) following administration of 250-500 mg/Kg for 1-2 h showed that time for peak plasma levels of phenylacetate and benzoate were similar as in adults.

The PK parameters of Ammonul™ in males and females were compared in study 951603. Group 1 (5.5 gm/m^2; N=3) had 2 males and 1 female while group 2 (3.75 gm/m^2; N=17) had 7 males and 10 females. PK parameters of benzoic acid and phenylacetate in males and females following NAPA/NABZ 3.75 gm/m^2 x 1.5 h are shown in Table 8. Both benzoic acid and phenylacetate AUC and C_{max} were approximately 21% higher in females than in males. Another PK study with increased number of subjects may be required to draw specific conclusions regarding gender effect.

Table 8 Benzoic acid and phenylacetate PK parameters in males and females following NAPA/NABZ 3.75 gm/m^2 x 1.5 h

Parameter	Benzoic Acid				Phenylacetate			
	N	Females	N	Males	N	Females	N	Males
AUClast(µg.hr/ml) Mean (SD)	10	618.3 (87.2)	7	487.8 (75.4)	10	2241.3 (209)	7	1753.9 (257.5)
C_{max} (µg/ml) Mean (SD)	10	284.0 (23.7)	7	221.8 (21.5)	10	332.2 (23.5)	7	260.2 (18.1)
CL (L/hr/m^2) Mean (SD)	10	4.39 (1.71)	7	6.34 (2.5)	10	1.61 (0.19)	7	2.11 (0.33)
T_{max} (hr) Mean (SD)	10	1.5 (0)	7	1.5 (0)	10	1.6 (0.2)	7	1.9 (0.4)
Vd (L/m^2) Mean (SD)	10	4.46 (1.99)	7	5.99 (2.19)	10	6.65 (1.24)	7	7.99 (1.05)

D. Extrinsic Factors

Drug-drug interaction

Sponsor has not conducted any drug-drug interaction studies with Ammonul™. No information is available on whether Ammonul™ is an inhibitor and/or inducer of any CYP450 enzyme(s). There are no reliable in vitro data to predict any in vivo drug-drug interaction. There is a drug interactions section under the Precautions in the label stating that drugs like penicillin, probenecid which alter renal excretion of many drugs may affect the excretion of hippurate and phenylacetylglutamine. But interaction potential between these drugs has not been evaluated.

E. General Biopharmaceutics

What is the formulation of Ammonul™?

Ammonul™ injection is a sterile product intended for parenteral administration. It contains two active ingredients, sodium phenylacetate and sodium benzoate dissolved in water for injection. No preservatives are added. If necessary, 1N hydrochloric acid and

sodium hydroxide solutions are used for pH adjustment. The unit and batch composition for the proposed batch size are shown in Table 9.

Table 9: Composition of Ammonul™

QUANTITATIVE COMPONENTS LISTING			
Component	Batch Formula	Percentage Formula (%)	Unit Formula (mg/mL)
Sodium Phenylacetate	[redacted]	10 %	100.0
Sodium Benzoate NF		10 %	100.0
1N Hydrochloric acid NF		N/A	N/A
1N Sodium hydroxide NF		N/A	N/A
Water for Injection USP		q.s 100%	q.s. 1 mL

*specific gravity = [redacted]

F. Analytical

What bioanalytical method was used to assess the plasma concentration?

An HPLC method using UV detection was used for the quantitative measurement of sodium phenylacetate (PAA), sodium benzoate (BZA) and their metabolites, phenylacetylglutamine (PAG) and hippurate (HIP) in plasma. The lower limit of quantitation was [redacted] for the parent as well as metabolites. The upper limit of quantitation was [redacted] for phenylacetylglutamine and hippurate while it was [redacted] for phenylacetate and benzoate. The recovery of phenylacetylglutamine, hippurate, sodium phenylacetate, and sodium benzoate from human plasma was approximately 95%, 91%, 100% and 94% respectively.

The results for accuracy and precision with quality control samples were acceptable. For example, mean accuracy (%CV) results ranged from 0.04- 12% and mean precision (%CV) ranged from 2.6-7.3% for quality control samples from study 951603. Table 10 shows the summary of statistics for quality control samples.

Table 10: Summary of statistics for quality control samples.

Summary of Statistics for Quality Control Samples												
Analyte:	PAG			HIP			PAA			BZA		
Nominal Concentration (ug/mL Plasma):	20.00	60.00	80.00	20.00	60.00	80.00	15.00	85.00	300.0	15.00	85.00	300.0
Number:	59	59	59	59	59	59	59	59	59	59	59	59
Mean:	19.81	61.77	80.56	17.65	54.30	73.26	13.96	84.04	295.9	14.44	83.16	300.1
Std. Dev.:	0.8650	2.274	2.165	1.125	3.944	4.390	0.5335	2.455	11.68	0.8923	2.405	11.73
Inaccuracy (%):	[redacted]											
Imprecision (%):												

8 Page(s) Withheld

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✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 1

IV. Appendix

A. Individual Study Reviews

Study 951603: Pharmacokinetic study of sodium phenylacetate/sodium benzoate administered as IV infusions in healthy adult volunteers.

Study Design: This study was done in order to characterize the pharmacokinetics of sodium phenylacetate (NAPA) and sodium benzoate (NABZ) when given together as a 1:1 solution (100 mg/ml) to normal healthy volunteers. For each active drug (NAPA and NABZ) and their respective metabolites (hippurate and phenylacetylglutamine) plasma concentrations-time profiles were generated at two dose levels (3.75 and 5.5 gm/m^2) following a single loading dose (period 1) (90 min) and a loading dose followed by a maintenance-dose infusion (period 2) over 24 hours. The 5.5 gm/m^{2}dose follows the current investigative drug administration labeling. There was a washout period of 7 days between the two periods. The dosing scheme is shown in Table 9.

Table 9: Study design

Number of Subjects and Gender	Period 1:	Period 2:	Comment
Group 1 (n=3)			
2 males 1 female	5.5 gm/m^2 x 90 minutes	5.5 gm/m^2 x 90 minutes followed by 5.5 gm/m^2 x 24 hours	pilot, period 1 and 2 in sequence
Group 2 (n=17)			
7 males 10 females	3.75 gm/m^2 x 90 minutes	3.75 gm/m^2 x 90 minutes followed by 3.75 gm/m^2 x 24 hours	period 1 and 2 in sequence

Study Results:

After administration of single loading dose:

The pharmacokinetic parameters for benzoic acid and phenylacetate are provided in Table 10 after the administration of 3.75 g/m^2 and 5.5 g/m^2 loading dose. Comparing the PK parameters between the two dose groups indicates that there is greater than dose

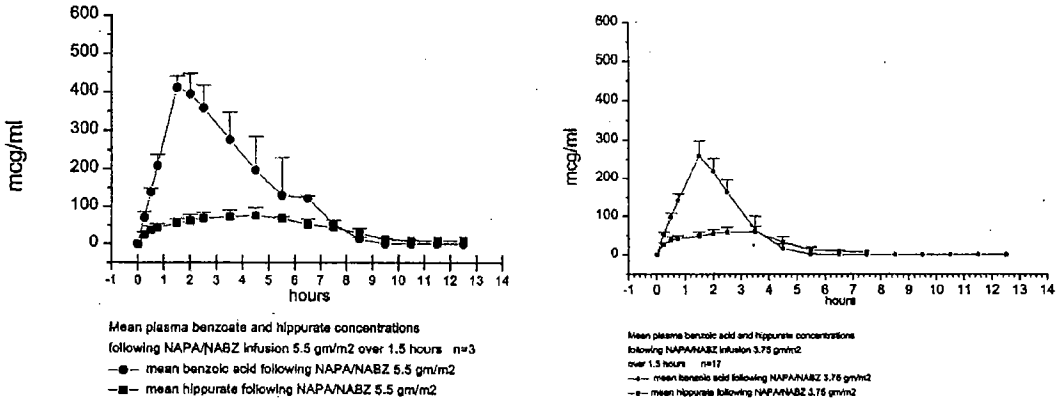
proportional increase in the AUClast and C_{max} for both benzoic acid and phenylacetate. The clearance of both these compounds decrease with an increase in dose.

Table 10: Benzoic acid and phenylacetate PK parameters following NAPA/NABZ 3.75 g/m^2 and 5.5 g/m^2 x 1.5 h

Parameter	Benzoic Acid				Phenylacetate			
	N	3.75 g/m^2	N	5.5 g/m^2	N	3.75 g/m^2	N	5.5 g/m^2
AUClast(µg.hr/ml) Mean (SD)	17	564.6 (103.9)	3	1599.1 (463.1)	17	2040.6 (332.5)	3	3829.2 (516.6)
C_{max} (µg/ml) Mean (SD)	17	258.4 (38.6)	3	416.7 (34.6)	17	302.6 (42.0)	3	411 (29.9)
CL ($L/hr/m^2$) Mean (SD)	17	5.19 (2.23)	3	3.62 (1.24)	17	1.82 (0.35)	3	0.89 (0.28)
T_{max} (hr) Mean (SD)	17	1.5 (0)	3	1.7 (0.3)	17	1.7 (0.3)	3	1.7 (0.3)
Vd (L/m^2) Mean (SD)	17	5.09 (2.15)	3	6.63 (0.96)	17	7.2 (1.32)	3	12.43 (0.62)

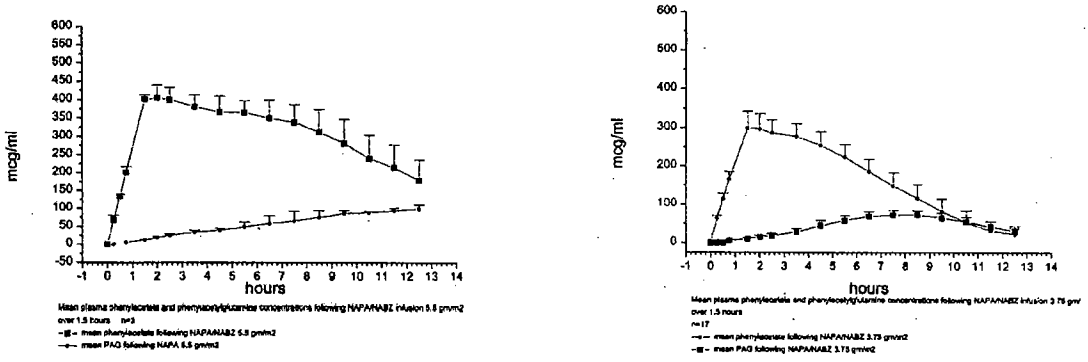
The mean plasma benzoic acid and hippurate concentrations following NAPA/NABZ infusion 5.5 g/m^2 and 3.75 g/m^2 are shown in Figure 5. As shown, following the single loading dose of NAPA/NABZ 3.75 g/m^2, plasma hippurate concentrations were detectable within 15 min from infusion start time and it increase rapidly. The hippurate concentration was lower than the parent in both the dosing groups. The hippurate was detectable in plasma for a longer time with the 5.5 g/m^2 dosing group than at the lower dose. The AUClast for hippurate was 236.8 µg.hr/ml and 516.3 µg.hr/ml for the 3.75 g/m^2 and 5.5 g/m^2 dose groups respectively.

Figure 5: Mean plasma benzoic acid and hippurate concentrations following NAPA/NABZ infusion 5.5 g/m^2 (left panel) and 3.75 g/m^2 (right panel)over 1.5 h.



The mean plasma phenylacetate and phenylacetylglutamine concentrations following NAPA/NABZ infusion 5.5 g/m^2 and 3.75 g/m^2 are shown in Figure 6. The plasma concentration time profile for phenylacetylglutamine appears quite different than that seen with hippurate. With the lower dose there were no detectable plasma phenylacetylglutamine concentrations till about 2 hr and then it increased gradually compared to hippurate. While in the higher dosing group, the concentrations increased over the entire sampling period. However till the last sampling period (12.5 h), there was no decline of the phenylacetylglutamine concentrations.

Figure 6: Mean plasma phenylacetate and phenylacetylglutamine concentrations following NAPA/NABZ infusion 5.5 g/m^2 (left panel) and 3.75 g/m^2 (right panel)over 1.5 h.



After administration of loading dose and continuous infusion over 25.5 hours:

The pharmacokinetic parameters for benzoic acid and phenylacetate are provided in Table 11 after the administration of 3.75 g/m^2 and 5.5 g/m^2 loading and continuous infusion over 25.5 h. For benzoic acid the Tmax was similar for both dose groups (1.5 h). In contrast, for phenylacetate the peak concentration was 2 h for the low dose and much later for the higher dose group (7.2 h). For both benzoic acid and phenylacetate there was greater than dose proportional increase in exposure.

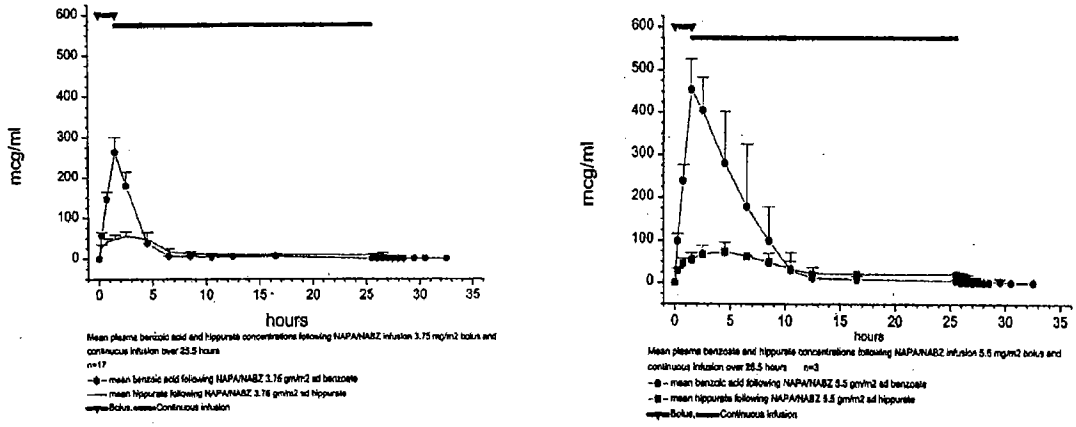
Table 11: Benzoic acid and phenylacetate PK parameters following NAPA/NABZ 3.75 g/m^2 and 5.5 g/m^2 priming and continuous infusion over 25.5 hours

Parameter	Benzoic Acid				Phenylacetate			
	N	3.75 g/m^2	N	5.5 g/m^2	N	3.75 g/m^2	N	5.5 g/m^2
AUClast(µg.hr/ml) Mean (SD)	14	737 (129.7)	3	2473.2 (878.7)	14	3532.5 (685.5)	3	8366.6 (1062)
Cmax (µg/ml) Mean (SD)	14	264 (36)	3	449.7 (159.8)	14	307.4(36.9)	3	465.4 (49.6)

Tmax (hr) Mean (SD)	14	1.5 (0)	3	1.5 (0)	14	2.0 (1.1)	3	7.2 (5.0)

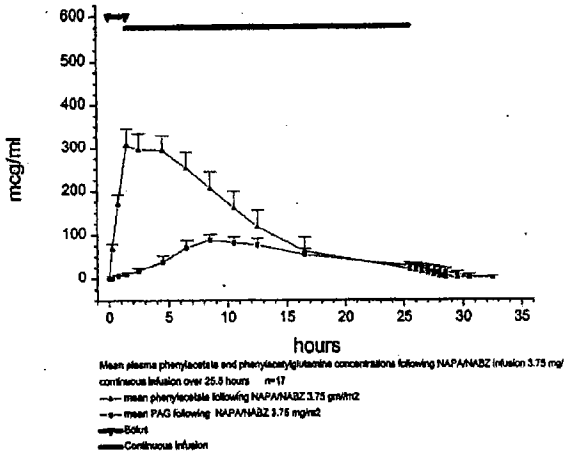
The mean plasma benzoic acid and hippurate concentrations following NAPA/NABZ 5.5 g/m^2 and 3.75 g/m^2 priming and continuous infusion over 25.5 hours over 25.5 hours are shown in Figure 7. Plasma benzoic acid levels continuously decline during the infusion period in both dose groups. Hippurate levels on the other hand increase above the benzoic acid concentration at around 5 h for the low dose and 10.5 h for the high dose groups.

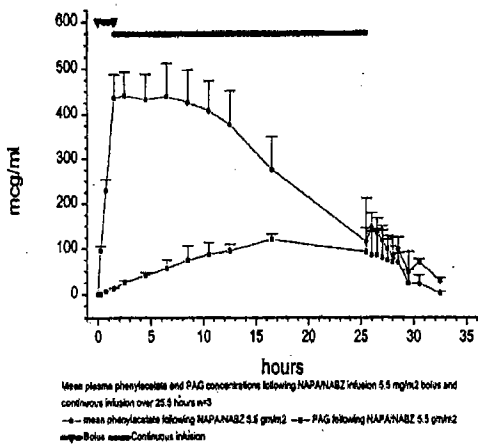
Figure 7: Mean plasma benzoic acid and hippurate concentrations following NAPA/NABZ infusion 3.75 g/m^2 (left panel) and 5.5 g/m^2 (right panel) priming and continuous infusion over 25.5 hours



The mean plasma phenylacetate and phenylacetylglutamine concentrations following NAPA/NABZ 5.5 g/m^2 and 3.75 g/m^2 priming and continuous infusion over 25.5 hours are shown in Figure 8. The peak phenylacetate concentration occurred later with the high dose and the duration of plateau during the infusion was much longer with the high dose. This phase was followed by a continuous decline in concentration.
Phenylacetylglutamine plasma concentration time profile was similar in both the dose groups.

Figure 8: Mean plasma phenylacetate and phenylacetylglutamine concentrations following NAPA/NABZ infusion 3.75 g/m^2 (left panel) and 5.5 g/m^2 (right panel) priming and continuous infusion over 25.5 hours





Overall Conclusions:

- Following the loading dose regimen both benzoic acid and phenylacetate demonstrated saturable elimination as evidenced by decreased clearance with increase in dose.
- There was greater than dose proportional increase in AUClast for both the compounds after the loading dose regimen.
- The formation of hippurate was more rapid than that of phenylacetylglutamine.
- The metabolite formation increased with dose for both the compounds after the loading dose regimen.
- During the loading dose with continuous infusion regimen plasma levels of benzoic acid declined following the loading dose, while phenylacetate levels remained unchanged initially during the infusion.
- Spot checking of data using non-compartmental analysis in WinNonlin resulted in similar PK parameters obtained by the sponsor.

Study 973600: Pharmacokinetic study of sodium phenylacetate/sodium benzoate administered as IV infusions (1 g/m^2, 2 g/m^2, 4 g/m^2) in healthy adult male volunteers.

Study Design: This was a 3-period escalating dose study in normal healthy male volunteers. The same dose of NAPA/NABZ was infused into all subjects during each dosing period (90 min). Plasma samples were obtained at 0, 0.25, 0.5, 0.75, 1.5, 2.5, 3.5, 4.5, 6.5, 7.5, 8.5, 9.5, 10.5, 11.5, 12.5, and 24 h.

Study Results:

The PK parameters for benzoic acid and phenylacetate are shown in Table 12. (N=6)

Table 12: Benzoic acid and phenylacetate PK parameters following NAPA/NABZ priming infusion over 1.5 hours

	Benzoic Acid	Phenylacetate

Parameter	1 g/m^2	2 g/m^2	4 g/m^2	1 g/m^2	2 g/m^2	4 g/m^2
AUClast(μg.hr/ml) Mean (SD)	20.3 (3.6)	114.9 (31.3)	562.8 (142.3)	175.6 (45.1)	713.8 (116.6)	2181.6 (249)
C_{max} (μg/ml) Mean (SD)	18.6 (4.1)	82.0 (18.4)	231.8 (25.5)	72.7(10.7)	173.4 (9.6)	306.5 (11.0)
T_{max} (hr) Mean (SD)	1.5 (0)	1.5 (0)	1.5 (0)	1.5 (0)	1.7 (0.3)	1.5 (0)

As shown above, benzoic acid AUC and Cmax increase in a greater than dose-proportionally manner. For phenylacetate there was a greater than dose-proportional increase in only AUC.

Sponsor also fit the data to a one-compartment model with Michaelis-Menten clearance and obtained the K_m and V_{max} values for benzoic acid and phenylacetate. The K_m and V_{max} of benzoic acid was 14.5 μg/ml and 94 mg/hr/l/m^2 and these values were very similar to that previously published in literature for healthy adults, 10.5 μg/ml and 101.9 mg/hr/l/m^2 respectively. Similarly, the K_m and V_{max} of phenylacetate was 36 μg/ml and 34.7 mg/hr/l/m^2. Values previously published in literature for phenylacetate in cancer patients were K_m (106 μg/ml) and V_{max} (29 mg/kg/h) respectively.

The sponsor has not provided the details of how the data was fit to Michaelis-Menten one-compartment model. Individual plasma concentration time profiles for the 6 subjects show that there was wide range of concentrations for the middle dose as compared to the lower and highest doses and therefore suggests that this dose might give a better estimate of K_m and V_{max}. The plasma concentration versus time data for both phenylacetate and benzoate after administration of 2 g/m^2 dose was analyzed using Michaelis-Menten one-compartment model in WinNonlin. The results for all the three doses are shown in the Table 13.

Table 13: Benzoic acid and phenylacetate pharmacokinetic parameters using Michaelis-Menten one-compartment model obtained by reviewer

Benzoic Acid							
Dose (g/m^2)	**K_m**	**Variance**	**V_{max}**	**Variance**	**V**	**Variance**	**N**
1	6.20	7.60	148.88	5305.15	6.92	6.75	6
2	19.26	114.31	117.12	950.06	10.17	0.52	6
4	32.61	198.32	104.59	593.72	11.33	0.19	6
Phenyl Acetate							
Dose (g/m^2)	**K_m**	**Variance**	**V_{max}**	**Variance**	**V**	**Variance**	**N**
1	40.29	7.36	51.8	7.24	9.07	0.32	6
2	23.09	8.26	38.21	5.09	8.89	0.141	6
4	4.72	2.12	28.4	1.68	10.91	0.085	6

The metabolite PK parameters are shown in Table 14 following a single loading dose. The Tmax of both hippurate and phenylacetylglutamine increased with increase in dose. The AUC for both increased proportionally with dose, while the increase in C_{max} appears to be slightly less than proportional to dose.

Table 14: Hippurate and phenylacetylglutamine PK parameters following NAPA/NABZ priming infusion over 1.5 hours (N=6)

Parameter	**Hippurate**			**Phenylacetylglutamine**		
	1 g/m^2	**2 g/m^2**	**4 g/m^2**	**1 g/m^2**	**2 g/m^2**	**4 g/m^2**
AUClast(μg.hr/ml) Mean (SD)	59.1 (13.7)	117.0 (37.6)	228.8 (48.1)	163.1 (26)	376 (60.3)	688.3 (52.2)
C_{max} (μg/ml) Mean (SD)	33.2 (6.0)	48.6 (14)	57.4 (17.3)	43.4(8.5)	66 (14.1)	91.4 (3.4)
T_{max} (hr) Mean (SD)	1.5 (0)	2.0 (0.3)	3.5 (0.6)	2.8 (0.5)	4.5 (0)	7.7 (1.6)

Conclusions:

- The highest dose used by sponsor in this study 4 g/m^2 was less than the normal adult dose 5.5 g/m^2. This was because the 5.5 g/m^2 dose was not tolerated by volunteers in the previous study (# 951603).
- The data were fit into a one-compartment model with Michaelis-Menten elimination.
- The dose of 2 g/m^2 gives a good estimate for the parameters K_m and V_{max}.

23 Page(s) Withheld

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✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 2

C. OCPB Filing Memo

1.1.1 Office of Clinical Pharmacology and Biopharmaceutics

2 *New Drug Application Filing and Review Form*

2.1.1.1.1 *General Information About the Submission*

	Information		Information
NDA Number	**20,645**	**Brand Name**	**Ammonul®**
OCPB Division (I, II, III)	**DPE-II**	**Generic Name**	**(Sodium phenylacetate/sodium benzoate 10%) injection**
Medical Division	**Metabolic and Endocrine Drug Products**	**Drug Class**	**Nutrients**
OCPB Reviewer	**Jaya bharathi Vaidyanathan, Ph.D.**	**Indication(s)**	**Treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle**
OCPB Team Leader	**Hae-Young Ahn, Ph.D.**	**Dosage Form**	**100 mg/ml sodium phenylacetate/ 100 mg/ml sodium benzoate Injection solution**
		Dosing Regimen	**Neonates; infants; young children: 250 mg/kg loading dose over 2 hr and 250 mg/kg maintenance dose over 24 hr. Older children; Adults: 5.5 g/m^2 loading dose over 2 hr and 5.5 g/m^2 maintenance dose over 24 hr.**
Date of Submission	**8/9/04**	**Route of Administration**	**Intravenous**
Estimated Due Date of OCPB Review		**Sponsor**	**Medicis Pharmaceutical Corporation**
PDUFA Due Date	**2/10/05**	**Priority Classification**	**P**
2.1.1.2 Division Due Date	**2/1/05**	**Submission**	**Electronic**

2.1.1.2.1.1.1.1 Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
2.2 Healthy Volunteers-				
single dose:	X	1	1	

multiple dose:	X	1	1	
2.2.1 Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		2	2	
2.2.1.1.1.1				
2.2.1.1.1.2 **Filability and QBR comments**				

2.2.1.2	"X" if yes	2.2.1.2.1.1.1.1 Comments
2.2.1.3 Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
2.2.1.4 Comments sent to firm ? 2.2.1.5		
QBR questions (key issues to be considered)	What are the pharmacokinetics parameters of sodium phenylacetate and sodium benzoate after iv administration?	
Other comments or information not included above		
Primary reviewer Signature and Date	Jaya bharathi Vaidyanathan	
Secondary reviewer Signature and Date	Hae-Young Ahn	

On August 9, 2004, Medicis Pharmaceutical Corporation submitted NDA 20-645 for Ammonul® (sodium phenylacetate/sodium benzoate 10%) injection. This is a resubmission and was refused to file previously on April 28, 1998 and October 5, 2000. Ammonul® was granted orphan drug status for the treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle.

There are 2 PK studies submitted in support of this application:

3) Study 951603: Pharmacokinetic study of sodium phenylacetate/sodium benzoate administered as IV infusions in healthy adult volunteers.
4) Study 973600: Pharmacokinetic study of sodium phenylacetate/sodium benzoate administered as IV infusions (1 gm/m^2, 2 gm/m^2, 4 gm/m^2) in healthy adult male volunteers.

The pharmacokinetic results of Ammonul® are summarized as follows:
Study 951603: Subjects received a loading dose of either, 3.75 gm/m^2 or 5.5 gm/m^2 once followed by a 24 hr sustaining infusion. Drug and metabolite PK was followed. After the priming dose, sodium phenylacetate demonstrated nonlinear kinetics. Clearance decreased from 1.82 ± 0.35 to 0.89 ± 0.28 L/h/ m^2 with increased dose. Sodium benzoate also demonstrated saturable elimination with decreased clearance with increased dose. No marked gender differences were observed.
Study 973600: Subjects received escalating loading dose once. Sodium benzoate displayed nonlinear PK, with C_{max} increasing disproportionately with dose. Sodium phenylacetate also had nonlinear PK. Hippurate was detected within 15 min while

phenylacetylglutamine was detected at 0.5 to 1.5 hr. Both of these metabolites increased proportionally with dose.

PK information for Ammonul® has also been included from various references in the literature.

The clinical trial formulation is similar to the commercial batch.

Conclusions:

NDA 20-645 is fileable.

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/s/

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1/25/05 03:39:10 PM
PHARMACOLOGIST

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