

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-645

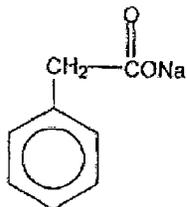
LABELING

1 **AMMONUL[®]**
2 (sodium phenylacetate and sodium benzoate) Injection
3 10% / 10%
4 Rx Only
5

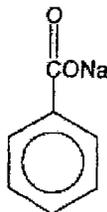
6 **DESCRIPTION**
7

8 AMMONUL[®] (sodium phenylacetate and sodium benzoate) Injection 10% / 10% is a
9 sterile, concentrated, aqueous solution of sodium phenylacetate and sodium benzoate, used
10 for the treatment of hyperammonemia in urea cycle disorders. The pH of the solution is
11 between 6 and 8. Sodium phenylacetate is a crystalline, white to off-white powder with a
12 strong, offensive odor. It is soluble in water. Sodium benzoate is a white and odorless,
13 crystalline powder that is readily soluble in water.
14

15 **Figure 1**



Sodium Phenylacetate



Sodium Benzoate

16
17 Sodium phenylacetate has a molecular weight of 158.13 and the molecular formula
18 $C_8H_7NaO_2$. Sodium benzoate has a molecular weight of 144.11 and the molecular formula
19 $C_7H_5NaO_2$.
20

21 Each mL of AMMONUL[®] contains 100 mg of sodium phenylacetate and 100 mg of
22 sodium benzoate, and Water for Injection. Sodium hydroxide and/or hydrochloric acid
23 may have been used for pH adjustment.
24

25 AMMONUL[®] injection is a sterile, concentrated solution intended for intravenous
26 administration via a central line only after dilution (see **DOSAGE AND**
27 **ADMINISTRATION**). AMMONUL[®] is packaged in single-use vials.
28

29 **CLINICAL PHARMACOLOGY**
30

31 Sodium phenylacetate and sodium benzoate are metabolically active compounds that can
32 serve as alternatives to urea for the excretion of waste nitrogen. Phenylacetate conjugates
33 with glutamine in the liver and kidneys to form phenylacetylglutamine, via acetylation.
34 Phenylacetylglutamine is excreted by the kidneys via glomerular filtration and tubular
35 secretion. The nitrogen content of phenylacetylglutamine per mole is identical to that of
36 urea (both contain two moles of nitrogen). Similarly, preceded by acylation, benzoate

37 conjugates with glycine to form hippuric acid, which is rapidly excreted by the kidneys by
38 glomerular filtration and tubular secretion. One mole of hippuric acid contains one mole
39 of waste nitrogen. It has been shown that phenylacetylglutamine and hippurate can serve
40 as alternative vehicles to effectively reduce waste nitrogen levels in patients with
41 deficiencies of urea cycle enzymes and, thus, attenuate the risk of ammonia and glutamine-
42 induced neurotoxicity.

43
44 Urea cycle disorders can result from decreased activity of any of the following enzymes:
45 *N*-acetylglutamate synthetase (NAGS), carbamyl phosphate synthetase (CPS),
46 argininosuccinate synthetase (ASS), ornithine transcarbamylase (OTC), argininosuccinate
47 lyase (ASL), or arginase (ARG). The most frequently observed initial presenting
48 symptoms in neonates include lethargy, seizures, poor feeding, neurologic changes,
49 edema, and respiratory distress. Patients with milder forms of enzyme deficiencies may
50 not present until late childhood, adolescence, or adulthood. Hyperammonemic crisis with
51 lethargy, delirium, and coma, in these patients, are often precipitated by viral illness, high
52 protein diet, stress, or trauma.

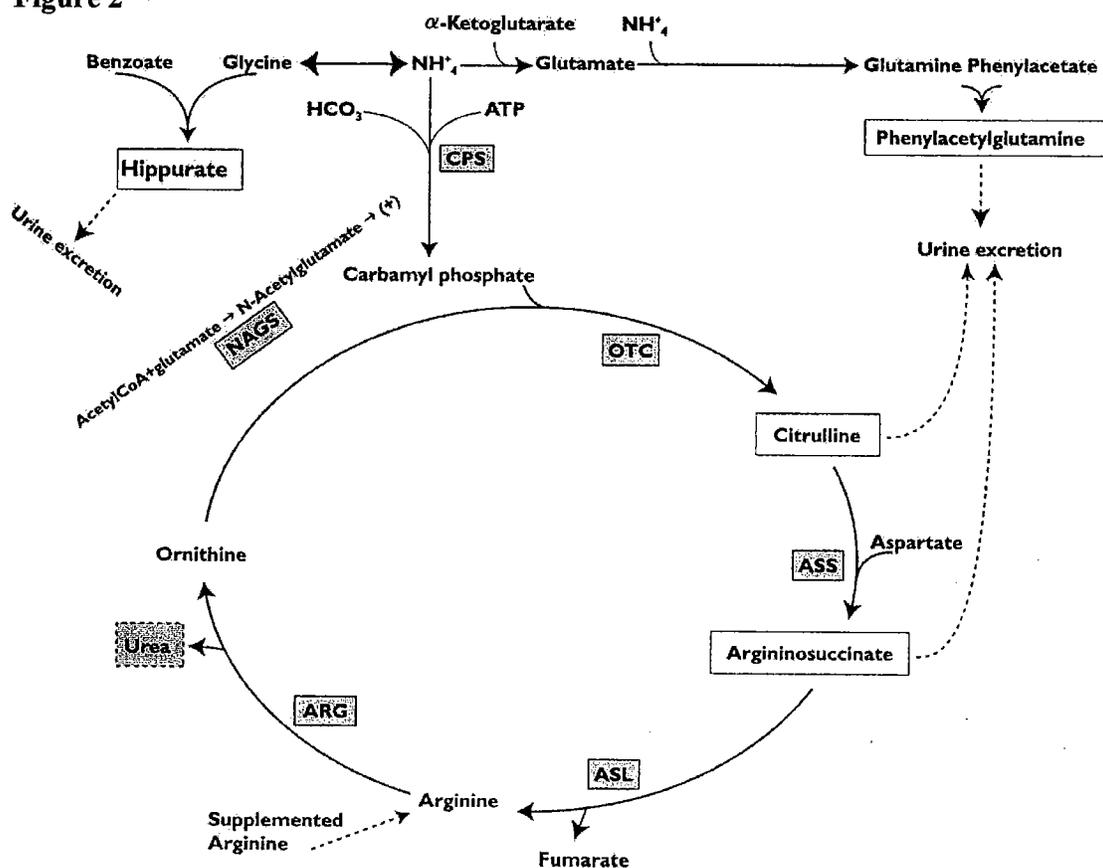
53
54 Plasma and urine amino acid analyses are used to diagnose ASS and ASL and to provide a
55 preliminary diagnosis of CPS, OTC, or ARG. Blood citrulline levels are very low or
56 absent in OTC and CPS, very high in ASS, and normal to moderately high in ASL and
57 ARG. ASL may be distinguished by the presence of high levels of the unusual amino acid
58 argininosuccinic acid (ASA) in the urine. It should be noted, however, that ASA tends to
59 co-elute initially with other amino acids (such as leucine and isoleucine) in
60 chromatographs, and may be missed on initial examination. ARG is characterized by high
61 urine levels of arginine. A definitive diagnosis of CPS and OTC require a liver biopsy, and
62 red blood cell enzyme analysis is needed to confirm a diagnosis of ARG. Patients
63 suspected of having a urea cycle disorder, based on family history, should have
64 documented hyperammonemia prior to administration of AMMONUL[®].

65 66 **Mechanism of Action**

67
68 Figure 2 is a schematic illustrating how the components of AMMONUL[®], phenylacetate
69 and benzoate, provide an alternative pathway for nitrogen disposal in patients without a
70 fully functioning urea cycle. Two moles of nitrogen are removed per mole of
71 phenylacetate when it is conjugated with glutamine, and one mole of nitrogen is removed
72 per mole of benzoate when it is conjugated with glycine.

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83 **Figure 2**



84
85
86 CPS = carbamyl phosphate synthetase; OTC = ornithine transcarbamylase; ASS = argininosuccinate synthetase; ASL =
87 argininosuccinate lyase; ARG = arginase; NAGS = N-acetylglutamate synthetase

88
89 **Pharmacokinetics**

90
91 The pharmacokinetics of intravenously administered AMMONUL[®] were characterized in
92 healthy adult volunteers. Both benzoate and phenylacetate exhibited nonlinear kinetics.
93 Following 90 minute intravenous infusion mean AUC_{last} for benzoate was 20.3, 114.9,
94 564.6, 562.8, and 1599.1 mcg/mL following doses of 1, 2, 3.75, 4, and 5.5 g/m²,
95 respectively. The total clearance decreased from 5.19 to 3.62 L/h/m² at the 3.75 and 5.5
96 g/m² doses, respectively.

97
98 Similarly, phenylacetate exhibited nonlinear kinetics following the priming dose regimens.
99 AUC_{last} was 175.6, 713.8, 2040.6, 2181.6, and 3829.2 mcg·h/mL following doses of 1, 2,
100 3.75, 4, and 5.5 g/m², respectively. The total clearance decreased from 1.82 to
101 0.89 mcg·h/mL with increasing dose (3.75 and 4 g/m², respectively).

102
103 During the sequence of 90 minute priming infusion followed by a 24 hour maintenance
104 infusion, phenylacetate was detected in the plasma at the end of infusion (T_{max} of 2 hr at
105 3.75 g/m²) whereas, benzoate concentrations declined rapidly (T_{max} of 1.5 hr at 3.75 g/m²)
106 and were undetectable at 14 and 26 h following the 3.75 and 4 g/m² dose, respectively.

107

108 A difference in the metabolic rates for phenylacetate and benzoate was noted. The
109 formation of hippurate from benzoate occurred more rapidly than that of
110 phenylacetylglutamine from phenylacetate, and the rate of elimination for hippurate
111 appeared to be more rapid than that for phenylacetylglutamine.

112

113 Pharmacokinetic observations have also been reported from twelve episodes of
114 hyperammonemic encephalopathy in seven children diagnosed (age 3 to 26 months) with
115 urea cycle disorders who had been administered AMMONUL[®] intravenously. These data
116 showed peak plasma levels of phenylacetate and benzoate at approximately the same times
117 as were observed in adults. As in adults, the plasma levels of phenylacetate were higher
118 than benzoate and were present for a longer time [1].

119

120 The pharmacokinetics of intravenous phenylacetate have been reported following
121 administration to adult patients with advanced solid tumors. The decline in serum
122 phenylacetate concentrations following a loading infusion of 150 mg/kg was consistent
123 with saturable enzyme kinetics. Ninety-nine percent of administered phenylacetate was
124 excreted as phenylacetylglutamine [2,3].

125

126 **Special Populations**

127

128 **Gender:**

129 Pharmacokinetic parameters of AMMONUL[®] were compared in healthy males and
130 females. Bioavailability of both benzoate and phenylacetate was slightly higher in females
131 than in males. However, conclusions cannot be drawn due to the limited number of
132 subjects in this study.

133

134 **Hepatic Insufficiency:**

135 Limited information is available on the metabolism and excretion of sodium phenylacetate
136 and sodium benzoate in patients with impaired hepatic function. However, as the liver is
137 one of the two organs (the other is the kidney) in which the metabolic conjugation of
138 sodium phenylacetate and sodium benzoate is known to take place, care should be used in
139 administering AMMONUL[®] to patients with hepatic insufficiency.

140

141 **Renal Impairment:**

142 For effective AMMONUL[®] drug therapy, renal clearance of the drug metabolites and
143 subsequently ammonia is required. Therefore, patients with impaired renal function
144 should be closely monitored.

145

146 **Dialysis:**

147 Intravenous use of AMMONUL[®] is complementary with the use of dialysis[4,5].
148 In the non-neonatal study patient population treated with AMMONUL[®], dialysis (standard
149 hemodialysis, peritoneal dialysis, arteriovenous hemofiltration, or other dialysis) was
150 required in 13% of hyperammonemic episodes. Standard hemodialysis was the most
151 frequently used dialysis method. High levels of ammonia can be reduced quickly when

152 AMMONUL[®] is used with dialysis, as the ammonia-scavenging of AMMONUL[®]
 153 suppresses the production of ammonia from catabolism of endogenous protein[6] and
 154 dialysis eliminates the ammonia and ammonia conjugates.
 155

156 **Drug Interactions:**

157 Formal drug interaction studies have not been performed with AMMONUL[®].
 158

159 **Pharmacodynamics**

160
 161 In patients with hyperammonemia due to deficiencies in enzymes of the urea cycle,
 162 AMMONUL[®] has been shown to decrease elevated plasma ammonia levels and improve
 163 encephalopathy and survival outcome compared to historical controls. These effects are
 164 considered to be the result of reduction in nitrogen overload through glutamine and glycine
 165 scavenging by AMMONUL[®] in combination with appropriate dietary and other supportive
 166 measures.
 167

168 **Clinical Data**

169
 170 The efficacy of AMMONUL[®] in improving patient survival of acute hyperammonemic
 171 episodes was demonstrated in an analysis of 316 patients (1045 episodes of
 172 hospitalization) treated between 1981 and 2003.
 173

174 The demographic characteristics and diagnoses of the patient population are shown in
 175 Table 1.
 176

177 **Table 1 Baseline Characteristics and Diagnoses of Study Population**

		Patients* N=316
Gender	Male	158 (51%)
	Female	150 (49%)
Age (years)	N	310
	Mean (SD)	6.2 (8.54)
	Min-Max	0.0-53.0
Age groups	0-30 days	104 (34%)
	31 days-2 years	55 (18%)
	> 2-12 years	90 (29%)
	> 12-16 years	30 (10%)
	> 16 years	31 (10%)
Enzyme deficiency	OTC	146 (46%)
	ASS	71 (22%)
	CPS	38 (12%)
	ASL	7 (2%)
	ARG	2 (< 1%)
	THN	2 (< 1%)
	Other**	56 (18%)

178 OTC = ornithine transcarbamylase deficiency; ASS = argininosuccinate synthetase deficiency; CPS =
 179 carbamyl phosphate synthetase deficiency; ASL = argininosuccinate lyase deficiency; ARG = arginase
 180 deficiency; THN = transient hyperammonemia of the newborn

181 *For the summary at the patient level, data obtained at first episode used.
182 **Diagnosis unknown or pending (33 episodes), acidemia (14 episodes), HHH syndrome (6 episodes),
183 carnitine translocase deficiency (4 episodes), liver disease (3 episodes), HMG CoA lyase deficiency (1
184 episode), non-ketotic hyperglycinemia (1 episode), suspected fatty acid oxidation deficiency (1 episode), and
185 valproic-acid-induced hyperammonemia (1 episode).

186
187 On admission to the hospital, patients with hyperammonemia or a potential urea cycle
188 disorder (UCD) were treated with a bolus dose of 0.25 g/kg (or 5.5 g/m²) sodium
189 phenylacetate + 0.25 g/kg (or 5.5 g/m²) sodium benzoate over a period of 90 minutes to 6
190 hours, depending on the specific UCD. Infusions also contained arginine; the dose of
191 arginine depended on the specific UCD. After completion of the bolus dose, maintenance
192 infusions of the same dose over 24 hours were continued until the patient was no longer
193 hyperammonemic or oral therapy could be tolerated. The mean (SD) duration of treatment
194 was 4.6 (6.45) days per episode, and ranged from 1 to 72 days.

195
196 Survival was substantially improved after Ammonul treatment compared with historical
197 values (estimated 14% 1-year survival rate with dietary therapy alone) [10] and with
198 dialysis (estimated 43% survival of acute hyperammonemia) [11].

199
200 Ninety-four percent (981 of 1045) of hyperammonemic episodes treated with
201 AMMONUL[®] resulted in patients being discharged from the hospital. Eighty percent of
202 patients (252 of 316) survived their last episode. Of the 64 patients who died, 53 (83%)
203 died during their first hyperammonemic episode. Of the 104 neonates (<30d) treated with
204 AMMONUL[®], 34 (33%) died during the first hyperammonemic episode.

205
206 Ammonia levels decreased from very high levels (> 4 times the upper limit of normal
207 [ULN]) to lower levels in 91% of episodes after treatment. In patients responding to
208 therapy, mean ammonia concentrations decreased significantly within four hours of
209 initiation of AMMONUL[®] therapy and were maintained. Dialysis is recommended for
210 those patients who fail to have a significant reduction in plasma ammonia levels within 4
211 to 8 hours after receiving AMMONUL[®]. A shift from high (≤ 4 times ULN) to very high
212 (> 4 times ULN) levels was observed in only 4% of the episodes.

213
214 Improvements in neurological status endpoints were observed in most episodes and
215 patients. Overall, investigators rated neurological status as improved, much improved, or
216 the same in 93% of episodes, and overall status in response to treatment as improved,
217 much improved, or the same in 97% of episodes. Recovery from coma was observed in
218 97% of episodes where coma was present at admission (111 of 114 episodes).

219

220

221

222 **INDICATIONS AND USAGE**

223

224 AMMONUL[®] is indicated as adjunctive therapy for the treatment of acute
225 hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes
226 of the urea cycle. In acute neonatal hyperammonemic coma, in moderate to severe

227 episodes of hyperammonemic encephalopathy, and in episodes of hyperammonemia which
228 fail to respond to an initial course of AMMONUL[®] therapy, hemodialysis is the most rapid
229 and effective technique for removing ammonia [12,13]. In such cases, the concomitant
230 administration of AMMONUL[®] can help prevent the re-accumulation of ammonia by
231 increasing waste nitrogen excretion [4,5,13].

232

233 CONTRAINDICATIONS

234

235 AMMONUL[®] should not be administered to patients with known hypersensitivity to
236 sodium phenylacetate or sodium benzoate.

237

238 WARNINGS

239

240 **Any episode of acute symptomatic hyperammonemia should be treated as a life-**
241 **threatening emergency. Treatment of hyperammonemia may require dialysis,**
242 **preferably hemodialysis, to remove a large burden of ammonia. Uncontrolled**
243 **hyperammonemia can rapidly result in brain damage or death, and prompt use of all**
244 **therapies necessary to reduce ammonia levels is essential.**

245

246 Management of hyperammonemia due to inborn errors of metabolism should be done in
247 coordination with medical personnel familiar with these diseases. The severity of the
248 disorder may necessitate the use of hemodialysis combined with nutritional management
249 and medical support. The multidisciplinary nature of the treatment usually requires the
250 facilities of a tertiary or quaternary care center.

251

252 Ongoing monitoring of plasma ammonia levels, neurological status, laboratory tests, and
253 clinical response in patients receiving AMMONUL[®] is crucial to assess patient response
254 to treatment. Because urine potassium loss is enhanced by the excretion of the non-
255 reabsorbable anions, phenylacetylglutamine and hippurate, plasma potassium levels should
256 be carefully monitored and appropriate treatment given when necessary. Serum
257 electrolyte levels should be monitored and maintained within the normal range.

258

259 AMMONUL[®] contains 30.5 mg of sodium per mL of undiluted product. Thus,
260 AMMONUL[®] should be used with great care, if at all, in patients with congestive heart
261 failure or severe renal insufficiency, and in clinical states in which there is sodium
262 retention with edema. If an adverse reaction does occur, discontinue administration of
263 AMMONUL[®], evaluate the patient, and institute appropriate therapeutic countermeasures.

264

265 **Administration must be through a central line. Administration through a peripheral**
266 **line may cause burns.**

267

268 Bolus infusion flow rates are relatively high, especially for infants (see **DOSAGE AND**
269 **ADMINISTRATION**). Extravasation of AMMONUL[®] into the perivenous tissues may
270 lead to skin necrosis. If extravasation is suspected, discontinue the infusion and resume at
271 a different infusion site, if necessary. Standard treatment for extravasation can include
aspiration of residual drug from the catheter, limb elevation, and intermittent cooling using

272 cold packs [14]. The infusion site must be monitored closely for possible infiltration
273 during drug administration. Do not administer undiluted product.

274
275 Due to structural similarities between phenylacetate and benzoate to salicylate,
276 AMMONUL[®] may cause side effects typically associated with salicylate overdose, such as
277 hyperventilation and metabolic acidosis. The clinician is advised to perform blood
278 chemistry profiles, and frequent blood pH and pCO₂ monitoring.

279 280 **PRECAUTIONS**

281 282 **General:**

283 AMMONUL[®] is a concentrated solution and must be diluted before administration via a
284 central line. Because sodium phenylacetate and sodium benzoate are metabolized in the
285 liver and kidney, and since phenylacetylglutamine and hippurate are primarily excreted by
286 the kidney, use caution when administering AMMONUL[®] to patients with hepatic or renal
287 insufficiency. AMMONUL[®] infusion has been associated with nausea and vomiting. An
288 antiemetic may be administered during AMMONUL[®] infusion.

289
290 **Because of prolonged plasma levels achieved by phenylacetate in pharmacokinetic**
291 **studies, repeat loading doses of AMMONUL[®] should not be administered.**

292
293 Use of corticosteroids may cause the breakdown of body protein and, thereby, potentially
294 increase plasma ammonia levels in patients with impaired ability to form urea.

295 296 **Neurotoxicity of Phenylacetate:**

297 Neurotoxicity was reported in cancer patients receiving intravenous phenylacetate,
298 250-300 mg/kg/day for 14 days, repeated at 4-week intervals. Manifestations were
299 predominantly somnolence, fatigue, and lightheadedness, with less frequent headaches,
300 dysgeusia, hypoacusis, disorientation, impaired memory, and exacerbation of a pre-
301 existing neuropathy. These adverse events were mainly mild. The acute onset of
302 symptoms upon initiation of treatment and reversibility of symptoms when the
303 phenylacetate was discontinued suggest a drug effect [2,3].

304
305 In animal studies, subcutaneous administration to rat pups of 190-474 mg/kg of
306 phenylacetate caused decreased proliferation and increased loss of neurons, and reduced
307 central nervous system (CNS) myelin. Cerebral synapse maturation was retarded, and the
308 number of functioning nerve terminals in the cerebrum was reduced, which resulted in
309 impaired brain growth [15]. Pregnant rats were given phenylacetate at 3.5 μmol/g/day
310 subcutaneous from gestation day 7 through normal delivery. Prenatal exposure of rat pups
311 to phenylacetate produced lesions in layer 5 cortical pyramidal cells; dendritic spines were
312 longer and thinner than normal and reduced in number [16].

313 314 315 316 **Drug Interactions:**

317 Some antibiotics such as penicillin may compete with phenylacetylglutamine and
318 hippurate for active secretion by renal tubules, which may affect the overall disposition of
319 the infused drug.

320

321 Probenecid is known to inhibit the renal transport of many organic compounds, including
322 aminohippuric acid, and may affect renal excretion of phenylacetylglutamine and
323 hippurate [13].

324

325 There have been reports that valproic acid can induce hyperammonemia through inhibition
326 of the synthesis of N-acetylglutamate, a co-factor for carbamyl phosphate synthetase [14].
327 Therefore, administration of valproic acid to patients with urea cycle disorders may
328 exacerbate their condition and antagonize the efficacy of AMMONUL® [15].

329

330 **Carcinogenesis, Mutagenesis, Impairment of Fertility:**

331 Carcinogenicity, mutagenicity and fertility studies of sodium phenylacetate have not been
332 conducted. Sodium benzoate has been extensively tested as a food preservative. Results
333 indicate that sodium benzoate is not mutagenic or carcinogenic, and does not impair
334 fertility.

335

336 **Pregnancy:**

337 Pregnancy Category C. Animal reproduction studies have not been conducted with
338 AMMONUL®. It is not known whether AMMONUL® can cause fetal harm when
339 administered to a pregnant woman or can affect reproduction capacity. Thus,
340 AMMONUL® should be given to a pregnant woman only if clearly needed.

341

342

343 **Labor and Delivery:**

344 The effects of AMMONUL® on labor and delivery are unknown.

345

346 **Nursing Mothers:**

347 It is not known whether sodium phenylacetate, sodium benzoate, or their conjugation
348 products are excreted in human milk. Because many drugs are excreted in human milk,
349 caution should be exercised when AMMONUL® is administered to a nursing woman.

350

351 **Pediatric:**

352 AMMONUL® has been used as a treatment for acute hyperammonemia in pediatric
353 patients including patients in the early neonatal period (see **DOSAGE AND**
354 **ADMINISTRATION**).

355

356 **ADVERSE REACTIONS**

357

358 The safety data were obtained from 316 patients who received AMMONUL® as
359 emergency (rescue) or prospective treatment for hyperammonemia as part of an
360 uncontrolled, open-label study. The study population included patients between the ages
361 of 0 to 53 years with a mean (SD) of 6.2 (8.54) years; 51% were male and 49% were

362 female who had the following diagnoses: OTC (46%), ASS (22%), CPS (12%), ASL
 363 (2%), ARG (< 1%), THN (< 1%), and other (18%).

364
 365 **Table 2 Adverse Events Occurring in \geq 3% of Patients Treated with Ammonul**

	Patients N=316
No. patients with any adverse event	163 (52%)
Blood and lymphatic system disorders	35 (11%)
Anemia NOS	12 (4%)
Disseminated intravascular coagulation	11 (3%)
Cardiac disorders	28 (9%)
Gastrointestinal disorders	42 (13%)
Diarrhea NOS	10 (3%)
Nausea	9 (3%)
Vomiting NOS	29 (9%)
General disorders and administration-site conditions	45 (14%)
Injection-site reaction NOS	11 (3%)
Pyrexia	17 (5%)
Infections	39 (12%)
Urinary tract infection NOS	9 (3%)
Injury, poisoning and procedural complications	12 (4%)
Investigations	32 (10%)
Metabolism and nutrition disorders	67 (21%)
Acidosis NOS	8 (3%)
Hyperammonemia	17 (5%)
Hyperglycemia NOS	22 (7%)
Hypocalcemia	8 (3%)
Hypokalemia	23 (7%)
Metabolic acidosis NOS	13 (4%)
Nervous system disorders	71 (22%)
Brain edema	17 (5%)
Coma	10 (3%)
Convulsions NOS	19 (6%)
Mental impairment NOS	18 (6%)
Psychiatric disorders	16 (5%)
Agitation	8 (3%)
Renal and urinary disorders	14 (4%)
Respiratory, thoracic and mediastinal disorders	47 (15%)
Respiratory distress	9 (3%)
Skin and subcutaneous tissue disorders	19 (6%)
Vascular disorders	19 (6%)
Hypotension NOS	14 (4%)

366

367 **Clinically Important Adverse Reactions**

368 Adverse events occurred most frequently in the following system organ classes: nervous
 369 system disorders (22% of patients), metabolism and nutrition disorders (21% of patients),
 370 and respiratory, thoracic and mediastinal disorders (15% of patients). The most frequently
 371 reported adverse events were vomiting (9% of patients), hyperglycemia (7% of patients),

372 hypokalemia (7% of patients), convulsions (6% of patients), and mental impairment (6%
373 of patients).

374

375 Adverse events leading to study drug discontinuation occurred in 4% of patients.
376 Metabolic acidosis and injection-site reactions each led to discontinuation in 2 patients
377 (< 1%). Adverse events leading to discontinuation in 1 patient included bradycardia,
378 abdominal distension, injection-site extravasation, injection-site hemorrhage, blister,
379 overdose, subdural hematoma, hyperammonemia, hypoglycemia, clonus, coma, increased
380 intercranial pressure, hypercapnia, Kussmaul respiration, respiratory distress, respiratory
381 failure, pruritis, and maculo-papular rash.

382

383 **Subpopulation and Risk Factor Data**

384

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

392

393 Adverse event profiles did differ by age group. Patients \leq 30 days of age had more blood
394 and lymphatic system disorders and vascular disorders (specifically hypotension), while
395 patients > 30 days of age had more gastrointestinal disorders (specifically nausea,
396 vomiting and diarrhea).

397

398 **Other Less Common Adverse Events Occurring in < 3% of Patients**

399 Less common adverse events that could represent drug-induced reactions or are
400 characterized as severe are listed below by body system.

401 BLOOD AND LYMPHATIC SYSTEM DISORDERS: coagulopathy, pancytopenia,
402 thrombocytopenia

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

405 EYE DISORDERS: blindness

406 GASTROINTESTINAL DISORDERS: gastrointestinal hemorrhage

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

409 HEPATOBILIARY DISORDERS: cholestasis, hepatic artery stenosis, hepatic failure/
410 hepatotoxicity, jaundice

411 INFECTIONS AND INFESTATIONS: sepsis/septic shock

412 INJURY, POISONING AND PROCEDURAL COMPLICATIONS: brain herniation,
413 subdural hematoma

414 INVESTIGATIONS: blood carbon dioxide changes, blood glucose changes, blood pH
415 increased, cardiac output decreased, pCO₂ changes, respiratory rate increased
416 METABOLISM AND NUTRITION DISORDERS: alkalosis, dehydration, fluid
417 overload/retention, hyperkalemia, hypernatremia, alkalosis, tetany
418 NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED: hemangioma acquired
419 NERVOUS SYSTEM DISORDERS: areflexia, ataxia, brain infarction, brain hemorrhage,
420 cerebral atrophy, clonus, depressed level of consciousness, encephalopathy, nerve
421 paralysis, intracranial pressure increased, tremor
422 PSYCHIATRIC DISORDERS: acute psychosis, aggression, confusional state,
423 hallucinations
424 RENAL AND URINARY DISORDERS: anuria, renal failure, urinary retention
425 RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS: acute respiratory
426 distress syndrome, dyspnea, hypercapnia, hyperventilation, Kussmaul respiration,
427 pneumonia aspiration, pneumothorax, pulmonary hemorrhage, pulmonary edema,
428 respiratory acidosis or alkalosis, respiratory arrest/failure
429 SKIN AND SUBCUTANEOUS TISSUE DISORDERS: alopecia, pruritis generalized,
430 rash, urticaria
431 VASCULAR DISORDERS: flushing, hemorrhage, hypertension,
432 phlebothrombosis/thrombosis
433

434 **OVERDOSAGE**

435

436 Overdosage has been reported during AMMONUL[®] treatment in urea cycle-deficient
437 patients [17]. All patients in the uncontrolled open-label study were to be treated at the
438 same dose of AMMONUL[®]. However, some patients received more than the dose level
439 specified in the protocol. In 16 of the 64 deaths, the patient received a known overdose of
440 AMMONUL[®]. Causes of death in these patients included cardiorespiratory failure/arrest
441 (6 patients), hyperammonemia (3 patients), increased intracranial pressure (2 patients),
442 pneumonitis with septic shock and coagulopathy (1 patient), error in dialysis procedure (1
443 patient), respiratory failure (1 patient), intractable hypotension and probable sepsis (1
444 patient), and unknown (1 patient). Additionally, other signs of intoxication may include
445 obtundation (in the absence of hyperammonemia), hyperventilation, a severe compensated
446 metabolic acidosis, perhaps with a respiratory component, large anion gap, hypernatremia
447 and hyperosmolarity, progressive encephalopathy, cardiovascular collapse, and death.
448

449 In case of overdose of AMMONUL[®], discontinue the drug and institute appropriate
450 emergency medical monitoring and procedures. In severe cases, the latter may include
451 hemodialysis (procedure of choice) or peritoneal dialysis (when hemodialysis is
452 unavailable) [17].
453
454
455

456 **DOSAGE AND ADMINISTRATION**

457

458 **Administration must be through a central line. Administration through a peripheral**
459 **line may cause burns.**

460

461 **General**

462

463 AMMONUL[®] is administered intravenously as a loading dose infusion administered over
464 90 to 120 minutes, followed by an equivalent maintenance dose infusion administered over
465 24 hours. AMMONUL[®] may not be administered by any other route. Administration of
466 analogous oral drugs, such as Buphenyl[®] (sodium phenylbutyrate), should be terminated
467 prior to AMMONUL[®] infusion.

468

469 Hyperammonemic coma (regardless of cause) in the newborn infant should be
470 aggressively treated while the specific diagnosis is pursued. All patients should be
471 promptly hemodialyzed as the procedure of choice using the largest catheters consistent
472 with the patient's size. A target blood flow of 150 mL/min/m² may be attained using a 7F
473 catheter. (Ammonia clearance [mL/min] is similar to the blood flow rate [mL/min] through
474 the dialyzer). Clearance of ammonia is approximately ten times greater by hemodialysis
475 than by peritoneal dialysis or hemofiltration. Exchange transfusion is ineffective in the
476 management of hyperammonemia. Hemodialysis may be repeated until the plasma
477 ammonia level is stable at normal or near normal levels.

478

479 AMMONUL[®] infusion should be started as soon as the diagnosis of hyperammonemia is
480 made. Treatment of hyperammonemia also requires caloric supplementation and
481 restriction of dietary protein. Non-protein calories should be supplied principally as
482 glucose (8-10 mg/kg/min) with Intralipid added. Attempts should be made to maintain a
483 caloric intake of greater than 80 cal/kg/d. During and after infusion of AMMONUL[®],
484 ongoing monitoring of neurological status, plasma ammonia levels, clinical laboratory
485 values, and clinical responses are crucial to assess patient response to treatment. The need
486 for other interventions to control hyperammonemia must be considered throughout the
487 course of treatment. Patients with a large ammonia burden or who are not responsive to
488 AMMONUL[®] administration require aggressive therapy including hemodialysis (see
489 WARNINGS).

490

491 AMMONUL[®] must be diluted with sterile Dextrose Injection, 10% (D10W) before
492 administration. The dilution and dosage of AMMONUL[®] are determined by weight for
493 neonates, infants and young children, and by body surface area for larger patients,
494 including older children, adolescents, and adults (Table 3). Maintenance infusions may be
495 continued until elevated plasma ammonia levels have been normalized or the patient can
496 tolerate oral nutrition and medications.

497

498 AMMONUL[®] solutions are physically and chemically stable for up to 24 hours at room
499 temperature and room lighting conditions. No compatibility information is presently
500 available for AMMONUL[®] infusion solutions except for Arginine HCl Injection, 10%,

501 which may be mixed in the same container as AMMONUL[®]. Other infusion solutions and
 502 drug products should not be administered together with AMMONUL[®] infusion solution.
 503 AMMONUL[®] solutions may be prepared in glass and PVC containers. AMMONUL[®]
 504 solutions should be inspected visually for particulate matter and discoloration before
 505 administration.
 506

507 **Table 3. Dosage and Administration**

Patient Population	Components of Infusion Solution		Dosage Provided		
	Ammonul	Arginine HCl Injection, 10%	Sodium Phenylacetate	Sodium Benzoate	Arginine HCl
AMMONUL [®] must be diluted with sterile dextrose injection 10% at ≥ 25 mL/Kg before administration.					
0 to 20 kg:					
CPS and OTC Deficiency					
Dose Loading: over 90 to 120 minutes Maintenance: over 24 hours	2.5 mL/kg	2.0 mL/kg	250 mg/kg	250 mg/kg	200 mg/kg
ASS and ASL Deficiency					
Dose Loading: over 90 to 120 minutes Maintenance: over 24 hours	2.5 mL/kg	6.0 mL/kg	250 mg/kg	250 mg/kg	600 mg/kg
> 20 kg:					
CPS and OTC Deficiency					
Dose Loading: over 90 to 120 minutes Maintenance: over 24 hours	55 mL/m ²	2.0 mL/kg	5.5 g/m ²	5.5 g/m ²	200 mg/kg
ASS and ASL Deficiency					
Dose Loading: over 90 to 120 minutes Maintenance: over 24 hours	55 mL/m ²	6.0 mL/kg	5.5 g/m ²	5.5 g/m ²	600 mg/kg

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Arginine Administration:

Intravenous arginine is an essential component of therapy for patients with carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), or argininosuccinate lyase (ASL) deficiency. Because a hyperchloremic acidosis may ensue after high-dose arginine hydrochloride administration, plasma levels of chloride and bicarbonate should be monitored and appropriate amounts of bicarbonate administered.

518

519 Pending a specific diagnosis, intravenous arginine (6 mL/kg of Arginine HCl Injection,
520 10%, over 90 minutes followed by the same dose over 24 hours) should be given to
521 hyperammonemic infants suspected of having a urea cycle disorder for two reasons:
522 1) infants with deficiencies in enzymes of the urea cycle (apart from arginase deficiency)
523 are usually arginine-deficient; 2) hyperammonemia in infants with ASS or ASL deficiency
524 usually respond favorably to arginine administration. If deficiencies of ASS or ASL are
525 excluded as diagnostic possibilities, the intravenous dose of arginine HCl should be
526 reduced to 2 mL/kg/d Arginine HCl Injection, 10%.

527

528 **Converting To Oral Treatment:**

529 Once elevated ammonia levels have been reduced to the normal range, oral therapy, such
530 as sodium phenylbutyrate, dietary management and protein restrictions should be started
531 or reinitiated.

532

533 **HOW SUPPLIED**

534

535 AMMONUL[®] (sodium phenylacetate and sodium benzoate) Injection 10% / 10% is
536 supplied in single-use glass vials.

537

538 NDC-62592-720-50 single use vial containing 50 mL of sodium phenylacetate and sodium
539 benzoate injection 10% / 10%.

540

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

542 **KEEP OUT OF REACH OF CHILDREN**

543 Non-pyrogenic.

544 Rx Only

545

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594 Manufactured by:
595 Chesapeake Biological Laboratories, Inc., 1111 South Paca Street, Baltimore MD 21230.

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599 Manufactured for:
600 Ucyclid Pharma, Inc., a wholly-owned subsidiary of Medicis Pharmaceutical Corp., 8125
601 North Hayden Road, Scottsdale, AZ 85258

602

603 Revision: February 2005



NDC 62592-720-50
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Ucecyld Pharma
NDC 62592-720-50

AMMONUL®
(sodium phenylacetate and sodium benzoate) Injection

100% / 10%

50 mL For IV use only

Warning: Administration must be through a central line. Administration through a peripheral line may cause burns. Must be diluted before IV administration. Sterile, non-pyrogenic, single use vial

Rx Only

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

KEEP OUT OF THE REACH OF CHILDREN

Manufactured for:
Ucecyld Pharma, Inc.
Scottsdale, AZ 85258

Manufactured by:
Chesapeake Biological Laboratories, Inc.
Baltimore, MD 21230

Dosage: See accompanying package insert.

Each mL of AMMONUL contains:
100 mg of sodium phenylacetate and 100 mg of sodium benzoate, and water for injection. Sodium hydroxide and/or hydrochloric acid may have been used for pH adjustment.

Sterile, concentrated solution must be diluted with sterile, deionized injection, 10% (D10W) before intravenous administration.

Lot No. Exp.

200%

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LINE
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 sodium benzoate) Injection

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 before intravenous administration.**

EXP:XXXX
 LOT:XXXX-X

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