

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20-645

MEDICAL REVIEW

Deputy Division Director/Team Leader Memo

NDA #: 20-645

Sponsor: Medicis

Drug name: Ammonul (sodium phenylacetate and sodium benzoate) 10%/10% for injection

Indication: Treatment of acute hyperammonemia in patients with urea cycle disorders

BACKGROUND

Urea cycle disorders are rare inborn errors of metabolism resulting from a deficiency of one of several enzymes involved in the removal of waste nitrogen. Depending on the enzyme affected and degree of deficiency, patients may present in the early neonatal period with a catastrophic illness or late childhood or adulthood after a precipitating event such as surgery, infection, trauma, pregnancy/delivery, or high protein intake that results in dangerously elevated blood ammonia levels. Patients with partial deficiencies may exhibit behavior or symptoms that mimics neurologic or psychiatric illnesses. Dr. Lubas's review has summarized the different enzyme deficiencies, their mode of inheritance, and clinical characteristics unique to some disorders. Table 1 summarizes the UCDs targeted for treatment with Ammonul.

Table 1. Urea Cycle Disorders

Disorder	Deficient Enzyme	Inheritance Pattern
Carbaryl phosphate synthetase deficiency	Carbaryl phosphate synthetase (CPS)	autosomal recessive
Ornithine transcarbamylase deficiency	Ornithine transcarbamylase (OTC)	X-linked
Citrullinemia	Arginosuccinate synthetase (ASS)	autosomal recessive
Argininosuccinic aciduria	Argininosuccinate lyase (ASL)	autosomal recessive
Argininemia	Arginase (ARG)	autosomal recessive
N-acetylglutamate synthetase deficiency	N-acetylglutamate synthetase (NAGS)*	autosomal recessive

*allosteric activator of CPS-1

Long-term management of these patients includes dietary protein restriction, arginine and citrulline supplementation, and oral drug therapy that provides an alternate path for waste nitrogen removal (see below). The acute management of hyperammonemic crisis targets rapid reduction of blood ammonia levels and appropriate supportive care. Delay in recognizing the underlying condition and resultant prolonged exposure to elevated ammonia levels increase the risk of permanent neurologic damage or death. In the neonatal period, dialysis – particularly, hemodialysis – is a very effective means of lowering ammonia levels. Protein feedings are discontinued and maximal calories are provided in the form of intravenous glucose and intralipids to reduce catabolism.

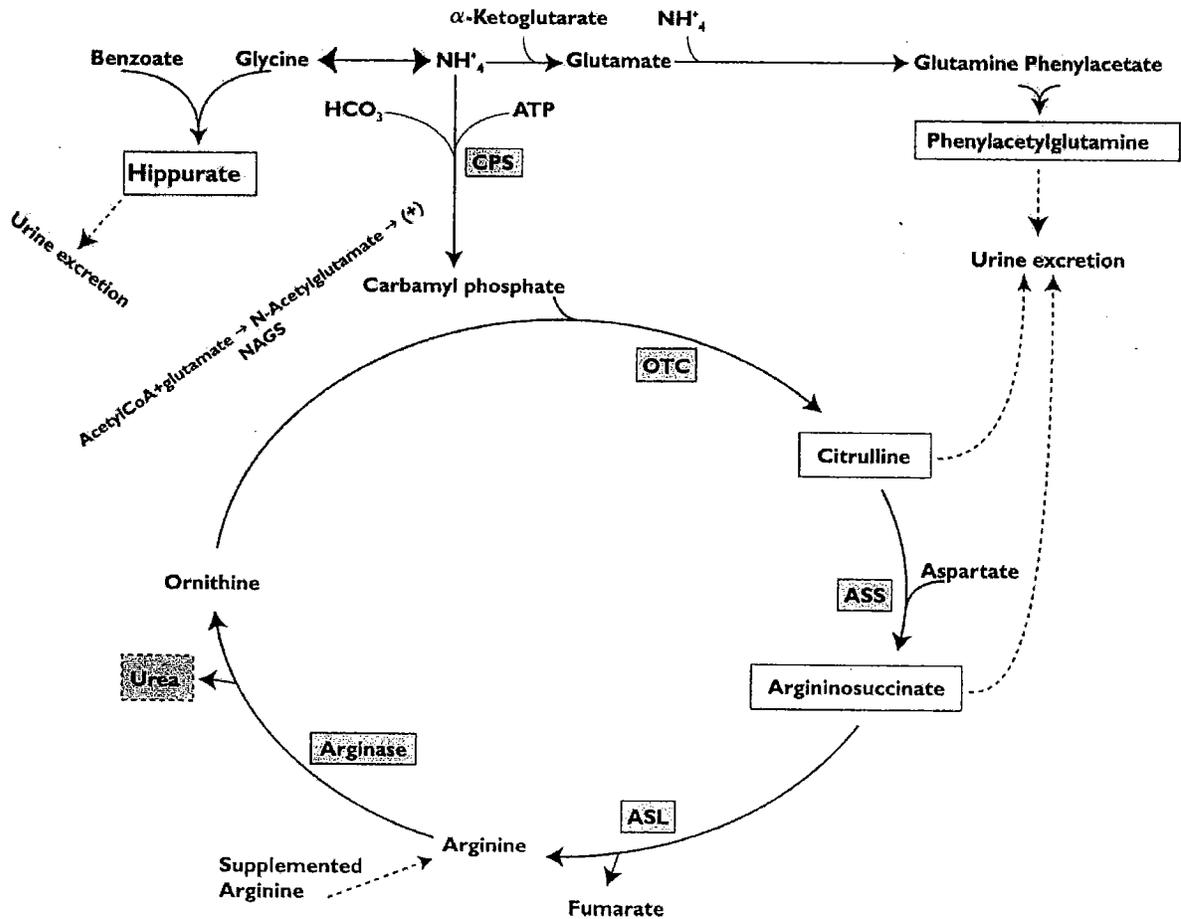
Alternative pathways for nitrogen excretion are utilized to further reduce ammonia levels.

Figure 1 summarizes the urea cycle, and the enzymes and substrates involved in nitrogen waste disposal. Arginine supplementation is administered to all patients presenting with hyperammonemia secondary to a UCD. For patients with deficiency in the enzyme, argininosuccinate lyase (ASL), arginine bypasses this site of enzymatic block allowing arginine to be converted to urea via arginase. Arginine can also be converted to the water soluble, citrulline, via ornithine transcarbamylase. Citrulline can then be excreted in the urine, allowing for another path of ammonia excretion. Arginine is also essential as patients with a UCD are likely deficient in this amino acid.

Figure 1 also shows sites of action for compounds developed to bypass enzyme deficiencies. The currently available oral therapy, sodium phenylbutyrate (Buphenyl®) is rapidly converted in the body to phenylacetate which conjugates with glutamine to form the water-soluble, phenylacetylglutamine. This by-product can be excreted in the urine allowing for the excretion of two moles of nitrogen per mole of phenylacetate. Another oral formulation that has been used in the past combines sodium phenylacetate and sodium benzoate (Ucephan®). Benzoate conjugates with glycine forming the water-soluble, hippuric acid, which can also be excreted in the urine. One mole of nitrogen is excreted in hippuric acid per mole of benzoate. This combination is not appealing to most patients because of the very strong, unpleasant odor of phenylacetate. Ucephan® is no longer available with manufacturing discontinued in 1998 for reasons other than safety. The disadvantage of both of these products is the oral route of administration which is not an acceptable route of treatment in patients in hyperammonemic crisis presenting with vomiting, obtundation, or seizures.

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Figure 1. Urea Cycle and Alternate Pathways for Waste Nitrogen Excretion



NAGS = N-acetylglutamate synthetase; CPS = carbamyl phosphate synthetase; OTC = ornithine transcarbamylase; ASS = argininosuccinate synthetase; ASL = argininosuccinate lyase

DESCRIPTION OF CLINICAL APPLICATION

Ammonul® is an intravenous formulation of 10% sodium phenylacetate and 10% sodium benzoate. The proposed indication is the acute treatment of hyperammonemia in patients with urea cycle disorders.

As discussed extensively in Dr. Lubas's review, this clinical development program involved a complex treatment protocol of critically ill patients including neonates (< 21 days of age) who presented with hyperammonemia. The program studied not only patients with different enzyme defects involved in the urea cycle but also included a small number of patients with hyperammonemia due to other causes. The age range of patients enrolled was from birth to 53 years of age. Patients with suspected UCD based on a family history of the disease but had no manifestation of the disease could enroll in the trial where they were treated prophylactically within the first 21 days of life. The

applicant misclassified these patients as "prospectively-treated" patients when in effect, all patients were prospectively treated. Only 5 patients comprised this category. This memo will refer to this group as "suspected but undiagnosed UCD patients".

The dosing regimen for patients was empirically derived from calculations of expected moles of ammonia excreted per mole of phenylacetate or hippuric acid produced. A loading dose over 90 to 120 minutes followed by an infusion of an equivalent dose over a 24 hr period was the recommended dosing regimen. The dose was calculated based on weight of the patient with newborns and children up to 20 kg dosed on a mg/kg basis while patients above 20 kg were dosed based on body surface area. The infusion was to be continued until ammonia levels fell within the normal range or oral therapy could be tolerated. Given the critical state of presentation in the neonate, the protocol required that hemodialysis be initiated in patients < 21 days of age. Intravenous arginine supplementation was also initiated in all patients.

Efficacy Findings

The data submitted included treatment response in 316 patients who received Ammonul in an open-label, compassionate use setting. Strict adherence to the dosing regimen was not observed in the majority of patients. Protocol deviations included no loading dose or an undetermined loading dose, inappropriate dosing, missing ammonia levels, and other reasons outlined in Dr. Lubas's review. Despite protocol-violations, there did not appear to be a marked difference in the primary endpoint, survival, when the data were analyzed by protocol-compliant versus non-compliant or modified-compliant. Consequently, this memo and the label does not make a distinction across these treatment groups for purposes of efficacy discussion.

The primary endpoint evaluated in this application was patient survival. Three hundred sixteen patients experienced 1,045 episodes of hyperammonemia requiring treatment with Ammonul. Compared to historical data, the survival rate was higher in these patients (80% survival; 252/316) than a cohort of 216 Japanese UCD patients followed between 1975 and 1995 (prior to iv therapy) who had a survival rate of 48%. Only 15% of the non-neonatal population treated with Ammonul required hemodialysis which would suggest that improved survival with Ammonul therapy is independent of hemodialysis. Despite hemodialysis requirement for neonates (<30 days), survival rate was lower in this group (67%) compared to patients > 30 days of age (87%).

The applicant also evaluated change in neurologic status in 123 episodes that had coma documented at admission. Of these, 90% (111/123) did not have documented coma at the time of discharge. Six patients who were admitted without a coma developed a coma at end of treatment; two expired and four were transferred to another hospital where follow-up status was not made available. Poor neurologic status at admission was higher in patients < 30 days of age reflecting more severe deficiency states.

Ammonul effectively reduced ammonia levels in those patients who presented with levels > 4x ULN. 91% of these patients had reductions < 4x ULN; 56% had reductions to < 1x ULN.

Other endpoint measures included initiation of hemodialysis in the non-neonatal patient population. The protocol specified the initiation of hemodialysis after 8 hours if a patient

had not responded to Ammonul therapy. The criteria for non-response included hyperammonemic encephalopathy or signs/symptoms of Ammonul overdose (e.g, obtundation in the absence of hyperammonemia, hyperventilation, severe compensated metabolic acidosis with a possible respiratory component, large anion gap, hypernatremia and hyperosmolarity, progressive encephalopathy, or cardiovascular collapse). Only 15% of the non-neonatal population (37/242) required hemodialysis, suggesting clinical effectiveness of Ammonul as the initial management of hyperammonemia in non-neonatal patients with UCDs. Careful monitoring is still recommended to ensure timely initiation of hemodialysis in patients who are non-responsive to Ammonul.

Safety Findings

Adverse events reported in this clinical database were complicated by the baseline critical medical condition of the patients which may reflect more the severity of the disease and complications of hyperammonemia than the side-effects of the drug. Nevertheless, severe adverse effects such as worsening neurologic status, metabolic disturbance including acid-base disorders, electrolyte abnormalities, hematologic and coagulation disorders, or hypotension necessitate close monitoring of patients' vital signs and laboratory data throughout drug administration.

Several safety concerns merit special discussion in drug labeling. First, Ammonul, its metabolites and ammonia are renally excreted. Consequently, patients with renal failure require concurrent management with dialysis, preferably hemodialysis. Caution should be used when administering Ammonul to patients with renal insufficiency. Caution should also be used when administering Ammonul to patients with hepatic impairment.

Given the large amount of sodium per mL of undiluted product (30.5 g), careful monitoring of volume status is recommended, particularly in patients with CHF, renal insufficiency, or sodium-retaining states.

Reports of severe infusion site reactions have prompted the applicant to recommend that the product be administered only through a central line.

This trial also evaluated Ammonul in "suspected but undiagnosed UCD patients". There were 5 such patients. From Dr. Lubas's review, there was no clear evidence of efficacy while these patients experienced clinically relevant adverse events including acid-base disorders, hypernatremia, hypokalemia, liver function tests abnormalities. Two subjects who died were subsequently found to not have a UCD. _____

Labeling

Labeling comments are summarized in all primary discipline reviews and labeling was negotiated and agreed-upon during a teleconference conducted on Friday, February 3, 2005.

Financial Disclosure

Reviewed by Dr. Lubas and found to be acceptable.

Other Review Disciplines

CMC, OCPB, Pharmacology/toxicology, and DMETS reviews completed. No pending deficiencies or phase 4 commitments requested.

Pediatric Requirements

The applicant has fulfilled pediatric requirements as the patient population for this indication is primarily a pediatric population and the clinical database reflects use of Ammonul in pediatric patients including neonates.

Phase 4 Commitments

No Phase 4 commitments are required. Dr. Lubas's review discusses Phase 4 requests for patient registries for off-label use in non-UCD patients, use in pregnant patients, and use in patients with hepatic and renal impairment. Dr. Lubas made these requests during a teleconference with the applicant on February 3, 2005. [REDACTED]

[REDACTED]

It should be noted that patient registries are limited as this is a voluntary database. Furthermore, the population of patients having non-UCD causes of hyperammonemia remains small and meaningful information from a patient registry will be further limited by this small sample size of uncontrolled use. It is reasonable to assume that these conditions and their treatment with Ammonul will be directed primarily by specialists in these rare inborn errors of metabolism. It is also reasonable to expect publication on case series, anecdotal experience, and cohort experience. The applicant is encouraged to facilitate collaborative data-gathering from all these experts in the field and was reminded that annual reports should include published literature that may cover the patient population mentioned in Dr. Lubas's request.

Given that these requests do not constitute Phase 4 commitments, the relevance of the information from these registries has been adequately conveyed to the applicant during the teleconference and no further recommendations are necessary in the approval letter.

RECOMMENDATION

In conclusion, Ammonul which is an intravenous formulation of sodium phenylacetate and sodium benzoate, combines two products that allow alternative pathways for the excretion of waste nitrogen. The product effectively lowers blood ammonia levels and appears to have improved survival outcome over historical control data. Adverse drug experiences reported may reflect the underlying critical illnesses; however, adverse experiences appeared higher in those patients who were given more than one loading dose or a higher maintenance dose than recommended. Hemodialysis remains a very effective treatment for hyperammonemia and patients not responsive to Ammonul should be considered for hemodialysis.

Ammonul should be approved for the treatment of hyperammonemia in patients who have urea cycle disorders.

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/s/

Mary Parks
2/16/05 01:14:49 PM
MEDICAL OFFICER

David Orloff
2/17/05 07:21:20 PM
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Concur with Dr. Parks' recommendation for approval of this
sodium phenylacetate/sodium benzoate injection for the treatment of
acute hyperammonemia in urea cycle disorders.

CLINICAL REVIEW

Application Type NDA 20645
Submission Number 001
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Reviewer Name William Lubas, MD-PhD
Review Completion Date February 9, 2005

Established Name Sodium Phenylacetate-Sodium
Benzoate Injection (10%-10%)
(Proposed) Trade Name Ammonul®
Therapeutic Class 3041480
Applicant Medicis Pharmaceutical Corp.

Priority Designation P

Formulation Injection
Dosing Regimen IV bolus over 90-120 minutes;
followed by IV maintenance therapy

Indication Treatment of Acute
Hyperammonemia and Associated Encephalopathy

Intended Population Patients with Urea Cycle
Disorders

Table of Contents

1 EXECUTIVE SUMMARY	5
1.1 RECOMMENDATION ON REGULATORY ACTION	5
1.2 RECOMMENDATION ON POSTMARKETING ACTIONS	5
1.2.1 Risk Management Activity	5
1.2.2 Required Phase 4 Commitments	5
1.2.3 Other Phase 4 Requests	5
1.3 SUMMARY OF CLINICAL FINDINGS	5
1.3.1 Brief Overview of Clinical Program	5
1.3.2 Efficacy	6
1.3.3 Safety	6
1.3.4 Dosing Regimen and Administration	7
1.3.5 Drug-Drug Interactions	8
1.3.6 Special Populations	8
2 INTRODUCTION AND BACKGROUND.....	9
2.1 PRODUCT INFORMATION	12
2.2 CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS	13
2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES	13
2.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS	13
2.5 PRESUBMISSION REGULATORY ACTIVITY	13
2.6 OTHER RELEVANT BACKGROUND INFORMATION	13
3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES.....	14
3.1 CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE)	14
3.2 ANIMAL PHARMACOLOGY/TOXICOLOGY	15
4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY	15
4.1 SOURCES OF CLINICAL DATA	15
4.2 TABLES OF CLINICAL STUDIES	16
4.3 REVIEW STRATEGY	16
4.4 DATA QUALITY AND INTEGRITY	16
4.5 COMPLIANCE WITH GOOD CLINICAL PRACTICES	17
4.6 FINANCIAL DISCLOSURES	17
5 CLINICAL PHARMACOLOGY.....	18
5.1 PHARMACOKINETICS	18
5.2 PHARMACODYNAMICS	18
5.3 EXPOSURE-RESPONSE RELATIONSHIPS	20
6 INTEGRATED REVIEW OF EFFICACY.....	20
6.1 INDICATION.....	20
6.1.1 Methods.....	20
6.1.2 General Discussion of Endpoints	20
6.1.3 Study Design	20
6.1.4 Efficacy Findings	23
6.1.5 Clinical Microbiology	26
6.1.6 Efficacy Conclusions	26
7 INTEGRATED REVIEW OF SAFETY.....	27
7.1 METHODS AND FINDINGS	27
7.1.1 Deaths	27

Clinical Review

{Insert Reviewer Name}

{Insert Application and Submission Number}

{Insert Product Trade and Generic Name}

7.1.2 Other Serious Adverse Events.....	28
7.1.3 Dropouts and Other Significant Adverse Events.....	28
7.1.4 Other Search Strategies.....	28
7.1.5 Common Adverse Events.....	28
7.1.6 Less Common Adverse Events.....	30
7.1.7 Laboratory Findings.....	30
7.1.8 Vital Signs.....	31
7.1.9 Electrocardiograms (ECGs).....	32
7.1.10 Immunogenicity.....	32
7.1.11 Human Carcinogenicity.....	32
7.1.12 Special Safety Studies.....	32
7.1.13 Withdrawal Phenomena and/or Abuse Potential.....	32
7.1.14 Human Reproduction and Pregnancy Data.....	32
7.1.15 Assessment of Effect on Growth.....	32
7.1.16 Overdose Experience.....	32
7.1.17 Postmarketing Experience.....	33
7.2 ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS.....	33
7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety.....	33
7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety.....	35
7.2.3 Adequacy of Overall Clinical Experience.....	35
7.2.4 Adequacy of Special Animal and/or In Vitro Testing.....	35
7.2.5 Adequacy of Routine Clinical Testing.....	36
7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup.....	36
7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study.....	36
7.2.8 Assessment of Quality and Completeness of Data.....	36
7.2.9 Additional Submissions, Including Safety Update.....	36
7.3 SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS.....	39
7.4 GENERAL METHODOLOGY.....	40
7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence.....	40
7.4.2 Explorations for Predictive Factors.....	40
7.4.3 Causality Determination.....	40
8 ADDITIONAL CLINICAL ISSUES.....	41
8.1 DOSING REGIMEN AND ADMINISTRATION.....	41
8.2 DRUG-DRUG INTERACTIONS.....	42
8.3 SPECIAL POPULATIONS.....	42
8.4 PEDIATRICS.....	42
8.5 ADVISORY COMMITTEE MEETING.....	43
8.6 LITERATURE REVIEW.....	43
8.7 POSTMARKETING RISK MANAGEMENT PLAN.....	43
8.8 OTHER RELEVANT MATERIALS.....	43
9 OVERALL ASSESSMENT.....	43
9.1 CONCLUSIONS.....	43
9.2 RECOMMENDATION ON REGULATORY ACTION.....	44
9.3 RECOMMENDATION ON POSTMARKETING ACTIONS.....	44
9.3.1 Risk Management Activity.....	44
9.3.2 Required Phase 4 Commitments.....	44
9.3.3 Other Phase 4 Requests.....	44
9.4 LABELING REVIEW.....	44
9.5 COMMENTS TO APPLICANT.....	46

Clinical Review
{Insert Reviewer Name}
{Insert Application and Submission Number}
{Insert Product Trade and Generic Name}

10 APPENDICES.....	47
10.1 REVIEW OF INDIVIDUAL STUDY REPORTS	47
10.2 LINE-BY-LINE LABELING REVIEW	47
REFERENCES	64

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

An approval action is recommended.

1.2 Recommendation on Postmarketing Actions

None.

1.2.1 Risk Management Activity

None.

1.2.2 Required Phase 4 Commitments

None.

1.2.3 Other Phase 4 Request

- Patient registry to follow off-label use of Ammonul in patients with non-Urea Cycle Disorders.
- Patient registry to follow safety and efficacy in patients with hepatic or renal insufficiency.
- Patient registry to follow pregnancy outcomes for women treated with Ammonul during pregnancy.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Ammonul was studied in an open-label, uncontrolled trial in patients with acute hyperammonemia due to Urea Cycle Disorders (UCDs) and in neonates potentially at risk for UCDs. Patients treated in this protocol included: rescue patients, infants ≤ 21 days old with or without a previous diagnosis of UCD; and older patients usually with a confirmed diagnosis of UCD who were hospitalized with acute hyperammonemia; and prospectively treated patients, infants ≤ 21 days old with a family history of UCD who were considered at risk for hyperammonemia due to UCD but did not have hyperammonemia at initial treatment. Because of the acute and serious nature of the episodes of hyperammonemia, no active or placebo-controlled studies were conducted. Data instead were compared to historical controls. A small number of patients who were hyperammonemic but did not have UCDs [e.g., patients with Transient

Clinical Review

{Insert Reviewer Name}

{Insert Application and Submission Number}

{Insert Product Trade and Generic Name}

hyperammonemia of the newborn (THN), hyperornithinemia-hyperammonemia and homocitrullinuria (HHH) syndrome, carnitine translocase deficiency, HMG CoA lyase deficiency, nonketotic hyperglycinemia, valproic acid induced hyperammonemia, fatty acid oxidation deficiency, liver disease, and acidemia] received treatment but were not included in the protocol-compliant, or modified-protocol compliant subgroups.

1.3.2 Efficacy

The survival rate for all patients was 80% with better results in patients with an established diagnosis of a UCD such as OTCD (80%), ASD (90%), CPSD (84%) and ALD (100%) compared to patients with undiagnosed disorders or nonUCD cause of hyperammonemia (62%). This is much improved over historical reports which showed an overall survival rate of 48% after the first hyperammonemic crisis observed in 216 Japanese patients between 1978 and 1995 prior to the development of IV therapy with sodium phenylacetate and sodium benzoate (Uchino et al. 1998).

The survival rate for infants under 30 days of age was $70/104=67\%$ compared to $207/237=87\%$ for subjects presenting after 30 days of age. This is compared to a historical rate of 43% and 75%, respectively, in historical controls (Uchino et al. 1998).

Survival rates were higher in female patients with OTCD (88%), most of whom probably had late-onset OTCD, compared to male patients with OTCD (71%), who may present with neonatal and infantile-onset OTCD. These rates are improved when compared to historical survival rates for neonatal OTCD, late onset disease in females, and males of 14%, 66%, and 59% respectively (Uchino et al. 1998).

Treatment with Ammonul was shown to lower plasma ammonia levels in 91% of patients with baseline values $> 4xULN$ and to improve the neurological status in 96% of patients for whom data were available. Dialysis was necessary to lower plasma ammonia levels in only 15% of all patients, excluding neonates who were required to get dialysis as part of the treatment protocol.

There was no clear evidence of efficacy in prospectively treated patients.

In summary, Ammonul is effective at lowering plasma ammonia levels, improving neurological status and limiting the need for dialysis in most UCD patients during episodes of acute hyperammonemia. However, there are insufficient data to support treatment of non-UCDs or to recommend prophylactic treatment of patients with suspected UCDs.

1.3.3 Safety

Common adverse events, serious adverse events (SAEs) and treatment-related adverse events were reported in 52, 34 and 34% of patients, respectively.

Gastrointestinal disorders, including nausea, vomiting and diarrhea, were more common in children over 30 days of life. Anti-emetic agents may be needed during the Ammonul infusion to prevent these adverse reactions.

Injection site reactions, including edema, erythema and hemorrhage were observed in the clinical study program. Since the drug product requires dilution with >25 mL/kg of D10W prior to IV administration, the flow rates can be too high to safely perfuse peripheral lines in small children, and, it is recommended that Ammonul be infused through a central line to avoid peripheral extravasations.

Ammonul contains a large amounts of sodium and must be diluted with >25 mL/kg of D10W, which can lead to fluid overload in patients with cardiac failure or renal insufficiency. Urine potassium loss is enhanced by the excretion of the non-reabsorbable anions (hippurate and phenylacetylglutamine). Arginine supplementation, which is an important component of treating hyperammonemia in UCDs, has been associated with hyperchloremic acidosis. Therefore, hypokalemia, hypernatremia, hyperglycemia, acidosis, hypertension and hypotension can occur during the management of hyperammonemia with Ammonul and arginine supplementation. Frequent monitoring of chemistry profiles, fluid status, blood pH, pCO₂, and vital signs in an intensive care setting is recommended.

Increased intracranial pressure and cerebral edema can be due to hyperammonemia or they can result from an overdose during the Ammonul infusion. Patients treated with Ammonul need regular neurological exams to monitor for changes in mental status. Seizures and mental status changes were observed more commonly in patients with OTCD and CPSD.

Patients treated with Ammonul experienced coagulopathy, thrombocytopenia, anemia and disseminated intravascular coagulation. It is uncertain if these are related to the primary underlying disorder and/or liver failure or related to the drug product itself. Patients liver function and hematological status need to be monitored during the acute illness.

In summary, patients receiving Ammonul therapy must be closely monitored for the following treatment- and/or disease-related adverse reactions: vomiting (8%), hypokalemia (6%), metabolic acidosis (3%), convulsions (3%), mental impairment (3%), anemia (3%), diarrhea (3%), nausea (3%), pyrexia (3%), hyperglycemia (3%), acidosis (2%), hypotension (2%), disseminated intravascular coagulation (2%), hypernatremia (2%), brain edema (2%), headache (2%), agitation (2%), respiratory alkalosis (2%), tachypnea (2%), rash (2%), diaper dermatitis (2%), and injection site reaction (2%).

1.3.4 Dosing Regimen and Administration

For patients with acute hyperammonemia due to ██████████ diagnosed UCD, Ammonul is administered intravenously as a loading dose infusion over 90 to 120 minutes, followed by an equivalent maintenance dose over 24 hours. Patients under 20 kg are dosed on a weight basis with 2.5 mL/kg of Ammonul. This supplies 250 mg/kg of sodium phenylacetate and 250 mg/kg

of sodium benzoate. Patients over 20 kg are dosed based on body surface area with 55mL/m² of Ammonul. This supplies 5.5 g/m² of sodium phenylacetate and 5.5 g/m² of sodium benzoate.

Pending a specific diagnosis intravenous arginine 6 ml/kg is given as a loading dose over 90 to 120 minutes followed by an equivalent dose over 24 hours. If deficiencies of ASS an ASL are ruled out as diagnostic possibilities the arginine dose can be reduced to 2 ml/kg/day.

1.3.5 Drug-Drug Interactions

No specific drug interaction studies were performed. However, the following medications could interfere with treatment and should be avoided:

- antibiotics such as penicillin could affect the overall disposition of the infused drug
- probenecid, may affect renal excretion of phenylacetylglutamine and hippurate
- corticosteroids, may cause breakdown of body protein and could potentially increase ammonia levels
- valproic acid and haloperidol have been reported to induce hyperammonemia

1.3.6 Special Populations

non-Urea Cycle Disorders (non-UCDs)-While a small number of patients with hyperammonemia due to non-UCDs were studied and did show some response to therapy, the number of these patients was too small to draw clear conclusions about efficacy. Additionally, there are no good historical controls for comparison. Therefore, continued clinical trials in such conditions are recommended and no recommendation about use of Ammonul in patients with non-UCDs can be made at this time.

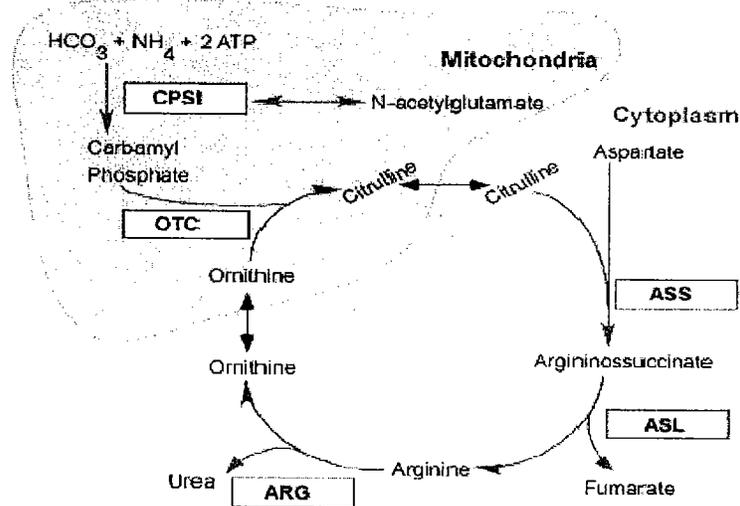
Renal Failure-There were five patients identified with renal insufficiency upon admission to the study. Hemodialysis was employed in two of the five patients but both of these patients died. For effective Ammonul drug therapy, renal clearance of the drug metabolites and subsequently ammonia is required. Therefore, patients with impaired renal function should be closely monitored.

Liver Failure- Limited information is available on the metabolism and excretion of sodium phenylacetate and sodium benzoate in patients with impaired hepatic function. Since metabolic conjugation of sodium phenylacetate and sodium benzoate is known to take place in the liver, care should be used in administering Ammonul to patients with hepatic insufficiency.

2 INTRODUCTION AND BACKGROUND

The urea cycle is a pathway of biochemical reactions that is responsible for the conversion of ammonia, a waste product from protein catabolism, into urea which can be safely removed from the body in urine (Brusilow S.W. and Horwich A.L.). Urea cycle disorders (UCDs) are inborn metabolic diseases resulting from a deficiency of any of the following enzymes: N-acetylglutamate synthetase (NAGS), carbamyl phosphate synthetase (CPS), argininosuccinate synthetase (AS or ASS), ornithine transcarbamylase (OTC), argininosuccinate lyase (ASL), or arginase (AG or ARG). The most common UCD is thought to be OTC deficiency (OTCD), followed by ASL deficiency (ASLD), while Arginase deficiency (AGD or ARGD) and NAGS deficiency (NAGSD) are considered the rarest.

Figure 1. The Urea Cycle



Source: Summa M.L. and Tuchman M.

It should be noted that hyperammonemia can also result from conditions other than UCDs, such as transient hyperammonemia of the newborn (THN), organic acidemias, and defects in transporter molecules, such as the ornithine transporter (resulting in hyperornithinemia, hyperammonemia, and homocitrullinuria [HHH] syndrome) or the dibasic acid transporter (resulting in lysinuric protein intolerance). Some patients with diagnoses other than UCDs were treated under this protocol pending a diagnosis.

At the Urea Cycle Consensus Conference in April 2000 it was estimated the incidence is 1 in 10,000 live births. The exact incidence of UCDs is unknown and probably underestimated, since many newborns die without definitive diagnoses. In many patients, especially those with severe deficits, the disease is observed soon after birth or in the first year of life. Patients

Clinical Review

{Insert Reviewer Name}

{Insert Application and Submission Number}

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developing symptoms within the first 30 days of life are considered neonatal-onset patients, and those developing symptoms during the first year are considered infantile-onset patients. Progressive hyperammonemia, if untreated or if treatment is ineffective, eventually results in cerebral edema, coma, and death. Generally, the more proximal the block in the urea cycle the more severe the disease. Thus, patients with complete CPSD or OTCD typically present during the first few days of life, while patients with ASD, ALD, AGD, or deficiencies in transporter molecules may present later in life. Patients with severe enzyme deficiencies typically develop symptoms within the first week of life, while patients with mild to moderate enzyme deficiencies may become symptomatic as children, and those with mild deficiencies may become symptomatic as adults.

Except for AGD, the clinical presentations of the UCDs are very similar, with symptoms resulting primarily from hyperammonemia. With neonatal presentation, the clinical course is usually catastrophic. Newborns typically appear normal at birth, and develop symptoms within the first week of life. Early symptoms are often nonspecific, including irritability, poor feeding, vomiting, hyperventilation, and somnolence, which progress to lethargy, loss of thermoregulation and hypothermia, and, if untreated, cerebral edema, coma, and eventually death. Other symptoms of hyperammonemia include hypotonia, poor growth, convulsions, disorientation, asterixis (rare), combativeness, obtundation, papilledema if cerebral edema and increased intracranial pressure are present, tachypnea or hyperpnea, apnea and respiratory failure, and in later stages, hepatomegaly, and decorticate or decerebrate posturing. If untreated or if treatment is ineffective, hyperammonemia presenting in the neonatal period is usually fatal. Patients who survive are often profoundly neurologically impaired and are at risk for future episodes of hyperammonemia throughout life.

Symptoms in older infants and children with moderate forms of these disorders may include hyperactivity with possible screaming and self-injurious behavior, avoidance of high-protein foods, episodic vomiting (especially after high-protein meals), developmental delays, and behavioral disturbances. These children may remain undiagnosed until they develop a hyperammonemic crisis with lethargy, delirium or coma, often precipitated by viral illness, high-protein meals, stress, or exhaustion. Other affected children may not have a hyperammonemic crisis, but may be mentally and neurologically impaired as a result of chronically elevated ammonia levels, and may be diagnosed during evaluation for mental retardation. Some patients with UCDs may not develop symptoms until adulthood, when they present with stroke-like symptoms, lethargy, and delirium, that may develop after childbirth, surgery, or other physiological stress or trauma. Such patients usually have milder disorders resulting from partial enzyme deficiencies. However, even these patients are at risk for hyperammonemic coma, which may be fatal or result in permanent neurologic damage.

Prompt, effective treatment is critical to prevent these outcomes. The degree of neurologic impairment has been shown to be correlated with the duration of hyperammonemic coma, and if ammonia levels exceed 5 times the upper limit of normal (ULN) (180 $\mu\text{mol/L}$) during hyperammonemic episodes, patients are at risk for severe neurological damage (Uchino T. et al. 1998). While the symptoms of ALD are generally similar to those of other UCDs, these patients are more likely to have hepatomegaly, and liver disease that may progress to cirrhosis. In

Clinical Review

{Insert Reviewer Name}

{Insert Application and Submission Number}

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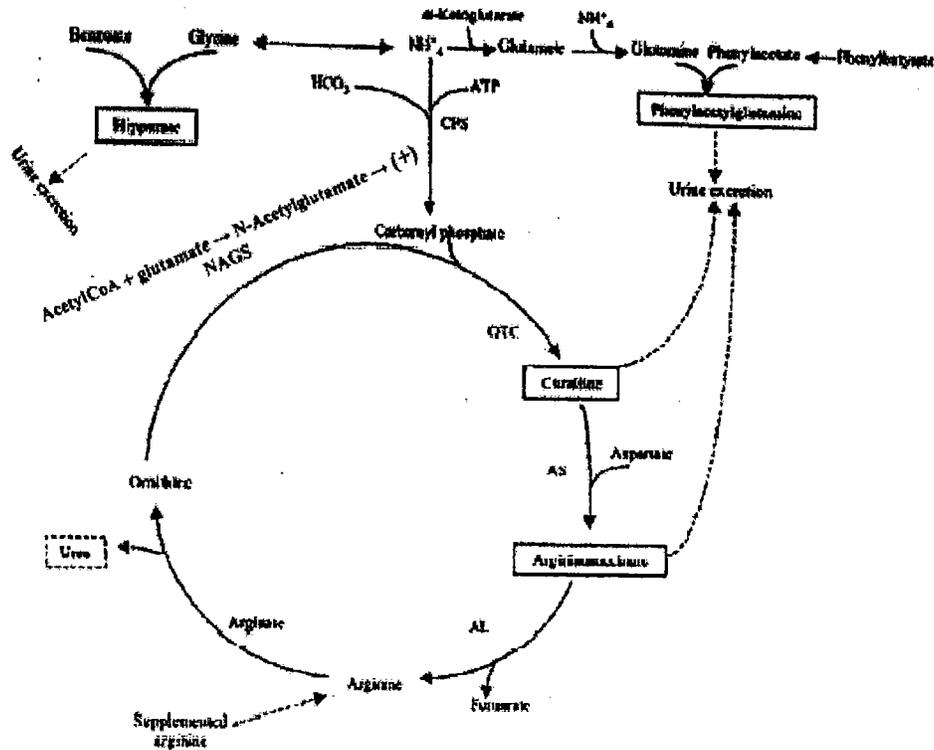
addition, these patients may have trichorrhexis nodosa (friable hair) or choreoathetotic movement disorder, which are not usually observed in the other UCDs.

The clinical presentation of AGD is slightly different and usually less catastrophic than that of the other UCDs for two reasons. First, arginine may be excreted in the urine, resulting in disposal of 2 waste nitrogen molecules, and second, there is an inducible isozyme of AG which catalyzes the same reaction located outside the liver which can mediate the formation of urea and ornithine from arginine, resulting in some functionality of the urea cycle. Neonatal hyperammonemic coma is less common in this disorder, and patients may present at an older age with spasticity, growth retardation, protein intolerance, and mental retardation. These patients may be misdiagnosed with cerebral palsy. While mortality is somewhat lower with this condition, patients are still at risk for severe hyperammonemic episodes.

All of the UCDs, except OTCD, are autosomal recessive conditions with a typical family history, if any, of affected siblings. OTCD is an X-linked disorder, with a typical history of affected male relatives on the maternal side of the family, and sometimes mild symptoms in the mother of the affected patient. Approximately 20% of carrier females develop symptoms. OTCD is the most common of the UCDs, and more than 140 different mutations in the gene for OTC have been identified. The OTC gene seems to have an unusually high rate of spontaneous mutation. At least 20 different variants of ASD and AGD have been identified, while fewer variants have been observed for CPSD, NAGSD, and ALD. Heterozygotes for the autosomal recessive conditions are often asymptomatic, although they may have low-level abnormalities of glutamine and urea metabolism that can be detected with testing.

Currently, patients with UCDs are managed chronically either by diet alone (primarily females with partial OTCD) or by dietary nitrogen restriction plus oral doses of sodium phenylbutyrate with citrulline or arginine. UCD patients treated with sodium phenylbutyrate may still experience episodes of hyperammonemic encephalopathy requiring hospitalization and immediate aggressive medical intervention. Ammonul, containing 10% sodium phenylacetate and 10% sodium benzoate, is proposed by the sponsor as adjunctive therapy for the treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in an enzyme of the urea cycle. The mechanism of action of this drug is shown in Figure 2. Conjugation of phenylacetate with glutamine, results in the removal of two moles of nitrogen per mole of phenylacetate, while conjugation of benzoate with glycine results in the removal of one mole of nitrogen per mole of benzoate. The end products of these reactions, phenylacetylglutamine (PAG) and hippurate, respectively, are low toxicity compounds that can be excreted in the urine and thereby provide an alternative pathway for nitrogen disposal.

Figure 2 Alternate Pathway for Nitrogen Disposal in Patients with UCDs Treated with Ammonul



Source: Summar M and Tuchman M. Proceedings of a consensus conference for the management of patients with urea cycle disorders. *J Pediatr* 2001 Jun;138(1):S6-10.

2.1 Product Information

Sodium Phenylacetate-Sodium Benzoate (10%-10%) is used as an adjunctive therapy for the treatment of acute hyperammonemia. It is supplied as a sterile solution in single-use, 50-mL vials containing 100 mg/mL sodium phenylacetate and 100 mg/mL sodium benzoate, and diluted with sterile 10% dextrose solution for IV administration. Dosing is dependent on the type of urea cycle disorder and weight or body surface area of the subject. Treatment includes an initial bolus over 1.5 to 2 hours followed by maintenance therapy of the same dose over the next 24 hours until the patient no longer has hyperammonemia or oral therapy can be tolerated.

2.2 Currently Available Treatment for Indications

Ucephan®, an oral formulation of sodium phenylacetate and sodium benzoate was approved to treat urea cycle disorders in 1987. It was discontinued from the market in 1997 for reasons other than safety.

Buphenyl®, sodium phenylbutyrate, a precursor to sodium phenylacetate was approved in 1996, and remains available as an oral maintenance therapy.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredients are currently available in the United States under an emergency IND.

2.4 Important Issues With Pharmacologically Related Products

Because of structural similarities between benzoate and salicylates, the potential exists for the side effects seen with benzoate to be similar to those of salicylates, such as exacerbation of peptic ulcers, mild hyperventilation, mild respiratory alkalosis, and possible edema due to sodium content. Oral sodium benzoate/sodium phenylacetate (Ucephan®), as well as sodium phenylbutyrate, which is converted to phenylacetate *in vivo*, have also been reported to deplete branched-chain amino acid levels in both UCD patients and healthy controls.

2.5 Presubmission Regulatory Activity

Treatment for UCDs with sodium benzoate and sodium phenylacetate was initiated under IND 17,123 in Feb 1986. The drug was initially developed as a chronic oral medication for UCD and the protocol was later amended to include IV use for episodic rescue from acute hyperammonemia. In April 1992, the product received FDA-orphan drug product designation which was transferred to Ucylyd Pharma. in Sept. 1997. In April 1999, the IND for IV use was also transferred to Ucylyd Pharma.

The first NDA for IV use for episodic rescue from acute hyperammonemia was submitted in Feb. 1998 and a refuse to file letter was issued because the majority of the data had been submitted in raw form with out adequate data analyses. The second NDA was submitted in June 2000 and a refuse to file letter was issued for inadequate data collection and failure to respond to the data analyses which had been previously requested by the Agency. This current NDA submission for this drug product was submitted in Aug. 2004. This time the NDA was accepted by the Agency and it was placed on a 6-month review time clock.

2.6 Other Relevant Background Information

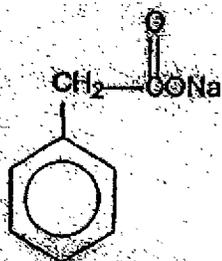
None.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

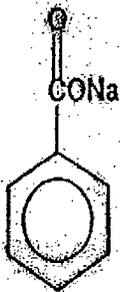
3.1 CMC (and Product Microbiology, if Applicable)

Ammonul is a sterile injectable new drug product formulation for intravenous administration containing:

10% Sodium Phenylacetate: Molecular Weight 158.1, Molecular Formula $C_8H_7NaO_2$
Sodium phenylacetate is a water soluble, crystalline, white to off-white powder with a strong offensive odor.



10% Sodium Benzoate: Molecular Weight 144.1, Molecular Formula $C_7H_5NaO_2$
Sodium benzoate is a water soluble, crystalline, white odorless powder.



See the Chemistry Review for additional information.

3.2 Animal Pharmacology/Toxicology

No non-clinical studies of phenylacetate or benzoate were conducted for this current application. Instead, the sponsor referenced previously published data on these compounds.

PHENYLACETATE-

The primary role of metabolism of phenylacetate in humans is by conjugation with glutamine in the liver and kidney. The product, phenylacetylglutamine, is then excreted in the kidney by glomerular filtration and secretion. In man, 91% of oral phenylacetate is conjugated with glutamine and excreted as phenylacetylglutamine, and only about 7% is conjugated to taurine.

Phenylacetate has been shown to effect the growth and differentiation of certain tumor cell lines and has been used in clinical trials in cancer patients.

Phenylacetate-induced neurotoxicity has been reported in immature rats models. Phenylacetate has been shown to inhibit mevalonate-5-phosphate decarboxylase, limiting the incorporation of mevalonate into lipids, sterols and polyprenols, and to inhibit cholineacetyltransferase decreasing levels of acetyl CoA.

BENZOATE-

Sodium benzoate is a food substance that has been used as a food preservative and is generally recognized as safe (GRAS). The primary role of metabolism of benzoate in humans is by conjugation with glycine in the liver and kidney. The product, hippuric acid, is then excreted in the kidney by glomerular filtration. There is no accumulation of benzoate in the body. When large amounts of benzoate are administered or when benzoate is given to patients with liver disease the compound can also be excreted as the benzoyl glucuronide.

There is no evidence of carcinogenicity following chronic administration of sodium benzoate in rats or mice.

See the Pharmacology/Toxicology Review for additional information.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The clinical data and study reports used in this review were submitted electronically and can be accessed at \\Cdseub1\N20645\N_000. The first set of data, referred to as "Group A", consisted of all patients/episodes analyzed and presented in the original NDA submission dated 29 June 2000 and included 108 patients and 354 episodes. The second set of data, referred to as "Group B" consisted of all patients/episodes since the original submission. These data had not been previously analyzed, and included 242 patients and 691 episodes. Some patients were included in both Groups A and B, so there was a total of 316 individual patients in this trial.

Clinical Review
 {Insert Reviewer Name}
 {Insert Application and Submission Number}
 {Insert Product Trade and Generic Name}

The study management differed between Group A and Group B episodes since the management of Ucylyd Pharma changed during that period. Additional data were collected from study sites and added to the database, including data from episodes that occurred prior to the previous submissions. Additionally, a comprehensive and systematic data management, capture, and evaluation process was implemented to improve analysis of data provided on both CRFs and source documents. Thus, better overall study management was provided for the Group B data.

4.2 Tables of Clinical Studies

Protocol	Design	Treatment groups	Treatment dose
Group A 354 episodes Group B 691 episodes	Open label, uncontrolled continuing study. Data was analyzed for protocol compliant and modified protocol compliant subgroups. Primary endpoint-survival Secondary endpoints-Neurological status, plasma ammonia levels, and need for dialysis	Hyperammonemia due to urea cycle disorders- Including ASD, OTCD, CPSD, ALD, AGD or unknown diagnosis	Sodium Phenylacetate/Sodium Benzoate 0.25 g/kg (<12y/o) or 5.5 g/m ² (>12y/o) Arginine 2-6mL/kg (<12y/o) or 4-12 g/m ² (>12y/o)

4.3 Review Strategy

This was an open label, uncontrolled single study for an orphan indication. There was no formal statistical analysis of efficacy. Data were compared to historical controls from the literature.

4.4 Data Quality and Integrity

There were no audits of study sites. Original CRFs were completed by site personnel or representatives of Ucylyd Pharma. [REDACTED] developed CRF addenda which attempted to capture some essential data which were not recorded on the original CRFs. Data clarification requests were handled within [REDACTED] source materials were consulted as needed for clarification. [REDACTED] did not contact study sites to resolve data issues. Upon generation of the tables, listings, and figures, each document underwent validation and verification processes per [REDACTED] standard operating procedures. In general, documents and datasets were validated using one or more of the following: independent

programming; comparisons of figures with supporting tables; comparisons of tables with supporting listings; or 100% verification of an appropriate sample.

4.5 Compliance with Good Clinical Practices

Because of the nature and seriousness of the disease being treated as well as the small number of patients with UCDs at each potential site, the sponsor did not attempt to train investigators in advance in protocol-specified procedures and applicable regulations. Therefore, deviations from procedures specified in the treatment guidelines were common. Some investigators did not submit the Form 1572 and some did not get approval from their IRBs. Attempts were made by Ucylyd Pharma to correct regulatory deviations (e.g., deviations from Good Clinical Practice, errors in informed consent procedures, etc.), but this was not always possible. In addition, it is known that investigators did not always follow the recommended study drug dosage and administration (see section 8.1) and/or did not complete case report forms properly. The protocol-compliant population was developed to address some of the concerns raised by the Division in the refusal-to-file letter dated October 05, 2000. Criteria for a modified protocol-compliant population were developed after discussions with the Division at a pre-NDA meeting in September 2003. After finalization of the statistical analysis plan, additional analyses of the OTCD group by gender and a "very high" category for ammonia values ($>4xULN$) were added.

4.6 Financial Disclosures

A total of 70 of the 107 investigators (65%) were certified as having no Financial Arrangement as defined in 21 CFR 54.2. A total of 35 of the investigators (33%) did not respond or could not be reached by the sponsor. Two investigators had financial information to disclose:

- Dr. [REDACTED] principle investigator of IND [REDACTED] the treatment and management of UCDs. The children of Dr. [REDACTED] previously owned 50% of [REDACTED] and will receive a lump sum payment from [REDACTED] upon approval of the NDA. Dr. [REDACTED] did not participate in the collection of the clinical data or interpretation of the study results.
- Dr. [REDACTED] received a \$100,000 donation toward the [REDACTED]. This grant was made in 2003 to create a national database where all patients with UCD can register. Since this contribution was made no more than [REDACTED] additional patients have been enrolled in the study according to the sponsor.

An analysis of the study sites found that only 189 of the 1045 episodes (18%) and 79 of the 351 patients (22%) reported in this study were from sites in which investigators had reported financial interests or did not submit financial disclosure forms. Eighteen of the 64 deaths (28%) observed in this study were at these sites. Therefore, there was a slightly higher mortality rate at these sites compared to the sites in which the clinical investigators had no documented financial interests. It is unlikely; therefore that the investigators, who had reported financial interests or did not submit financial disclosure forms, had biased the study results in favor of Ammonul.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Two studies in healthy adult volunteers were conducted. Both phenylacetate and benzoate exhibited nonlinear saturable elimination with a decrease in clearance and an increase in AUC with increased dose. Plasma hippurate was detected within 15 minutes of the start of the infusion and peaked at 2.5 to 5.5 hours. Plasma phenylacetylglutamate was detected within 30 minutes to 2 hours after the start of the infusion and peaked at 2.8 to 12.5 hours. There was no difference between males and females.

See the Pharmacokinetics/Pharmacodynamics Review for additional information.

5.2 Pharmacodynamics

Conjugation of phenylacetate with glutamine, and benzoate with glycine results in an alternative pathway for nitrogen disposal. The pharmacodynamic relationship between intravenous dosing with Ammonul and drop in mean plasma ammonia levels in both compliant and non-compliant episodes in this clinical study are shown in Figures 3 and 4, respectively. In both cases substantial drops in mean ammonia levels ($> 50 \mu\text{mol/L}$) can be seen within 4 hours after the start of the infusion.

**Appears This Way
On Original**

Figure 3

Plot of Mean Change in Plasma Ammonia in Protocol Compliant Episodes

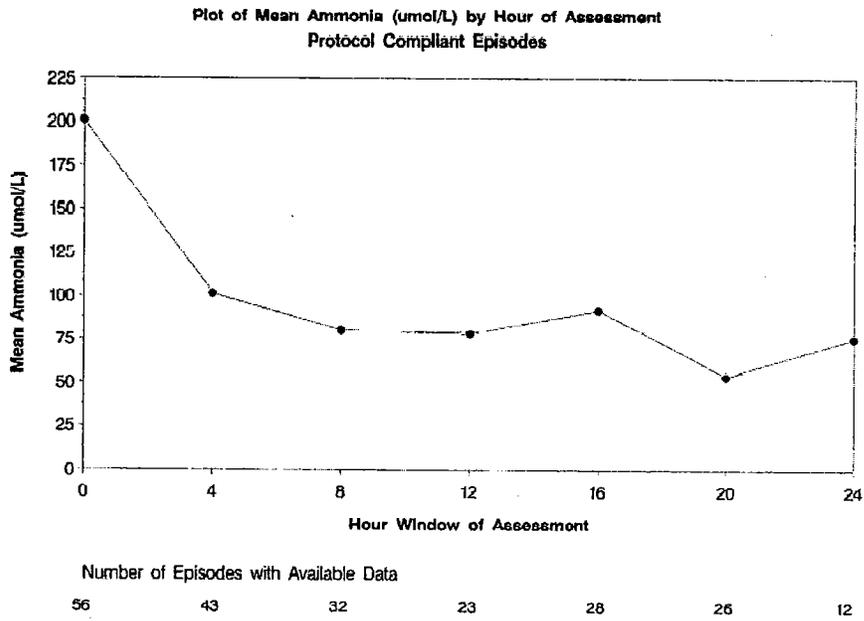
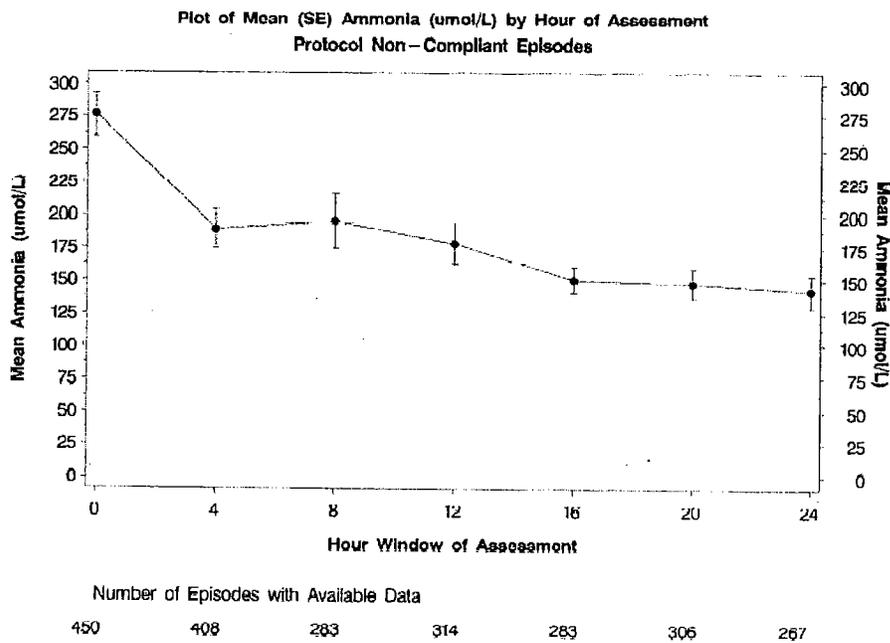


Figure 4

Plot of Mean Change in Plasma Ammonia in Protocol Non-Compliant Episodes



5.3 Exposure-Response Relationships

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 phenylacetylglutamine and hippurate derived from 24-hour infusion of the drug. Formal Phase II studies for emergency treatment of hyperammonemia in patients with UCDs were not submitted and are not ethical as these are life-threatening conditions which need immediate and rapid reduction in ammonia levels.

Phase II studies in cancer patients have shown dose-limiting toxicity due to neurocortical effects including somnolence and confusion and metabolic effects including hypokalemia, hyponatremia and hyperuricemia at IV doses above 410mg/kg/day for 5 days.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Treatment of acute hyperammonemia and associated encephalopathy in patients with Urea Cycle Disorders.

6.1.1 Methods

The clinical data and study reports reviewed in this submission were submitted electronically and can be accessed at [\\Cdsub1\N20645\N_000](#).

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint was survival status, which is a well accepted clinical endpoint.

Secondary efficacy endpoints included:

- Neurological status
- Plasma ammonia levels
- Number and percent of patients requiring dialysis, excluding neonatal rescue patients who were required to receive dialysis as part of the treatment protocol

6.1.3 Study Design

This is an open-label, uncontrolled study in patients with acute hyperammonemia due to UCDs and in neonates potentially at risk for UCDs. Patients treated in this protocol included rescue

Clinical Review

{Insert Reviewer Name}

{Insert Application and Submission Number}

{Insert Product Trade and Generic Name}

patients, infants ≤ 21 days old with or without a previous diagnosis of UCD, or older patients usually with a confirmed diagnosis of UCD who were hospitalized with hyperammonemia, and prospectively treated patients, infants ≤ 21 days old with a family history of UCD who were considered at risk for hyperammonemia due to UCD but did not have hyperammonemia at initial treatment. Only patients with a confirmed UCD diagnosis were considered compliant with the protocol. Because of the acute and serious nature of the episodes of hyperammonemia no active or placebo-controlled studies were conducted. Data were compared to historical controls. Some patients who were hyperammonemic but did not have UCDs [e.g., patients with Transient hyperammonemia of the newborn (THN), hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome, carnitine translocase deficiency, HMG CoA lyase deficiency, nonketotic hyperglycinemia, valproic acid induced hyperammonemia, fatty acid oxidation deficiency, liver disease, and acidemia] received treatment but were not included in the protocol-compliant, or modified-protocol compliant subgroups.

Each hospitalization for rescue or prospective treatment was considered an episode. Many patients were treated multiple times as rescue patients.

On the day of admission, patients with a previous or suspected diagnosis of UCD were treated with 250 mg/kg (or 5.5 g/m²) of sodium benzoate and 250 mg/kg (or 5.5 g/m²) sodium phenylacetate over 90 to 120 minutes except for suspected ASD in which case a 6-hour infusion was started at birth. Arginine was included in infusions at 200 mg/kg except for suspected ASS or ASL in which case a 600 mg/kg infusion was used. After completion of the bolus dose, maintenance infusions of the same dose of Ammonul and arginine over 24 hours were continued until the patient was no longer hyperammonemic or oral therapy could be tolerated. Neonatal rescue patients without a confirmed UCD diagnosis were to be treated first with arginine and hemodialysis, pending a diagnosis. Hemodialysis was recommended in all cases for patients not responding to treatment - i.e., no significant decrease in plasma ammonia levels after 8 hours of treatment, who developed hyperammonemic encephalopathy or showed signs of overdose (e.g, obtundation in the absence of hyperammonemia, hyperventilation, severe compensated metabolic acidosis with a possible respiratory component, large anion gap, hypernatremia and hyperosmolarity, progressive encephalopathy, or cardiovascular collapse).

Blood samples were collected for measurement of amino acid levels, clinical chemistry, ammonia, blood pH and pCO₂. Neurological status, including coma status, was evaluated on admission and at discharge. Argininosuccinate synthetase deficiency (citrullinemia) was diagnosed by the presence of high citrulline levels, while OTC and/or CPS deficiency was diagnosed by undetectable or trace citrulline levels, together with elevated urinary orotate in OTC deficiency. Liver biopsy was sometimes needed to confirm a diagnosis. In rescue patients with confirmed diagnoses, ondansetron (0.15 mg/kg) may have been used during the first 15 minutes of the priming infusion to prevent vomiting.

Treatment guidelines were not followed by all investigators. Episodes meeting any of the following criteria were considered to be noncompliant with the study protocol:

Clinical Review

{Insert Reviewer Name}

{Insert Application and Submission Number}

{Insert Product Trade and Generic Name}

- Overdose (> 250 mg/kg or > 5.5 g/m² for bolus dose; > 250 mg/kg/day or > 5.5 g/m²/day for maintenance dose). To control for rounding, values that fell within 0.24 to 0.26 g/kg and 5.4 to 5.6 g/m², were considered to meet the criteria.
- No bolus dose received
- Greater than one bolus dose except in patients undergoing dialysis (According to the consensus statement prepared by the UCD Conference Group, multiple bolus doses are acceptable for neonates undergoing dialysis.)
- Undetermined bolus dose
- No *abnormal* baseline plasma ammonia value available within 24 hours prior to the start of infusion for rescue patients
- No baseline plasma ammonia value available within 2 hours prior to the start of infusion for prospectively-treated patients
- Incorrect bolus or maintenance doses administered (not 250 mg/kg or 5.5 g/m² for bolus dose; not 250 mg/kg/day or 5.5 g/m²/day for maintenance dose)
- Unknown infusion duration or inadequate infusion information
- Unknown UCD diagnosis or diagnosis other than UCD
- Maintenance dose given prior to bolus dose
- Undetermined maintenance dose
- No maintenance dose

Episodes meeting any of the following criteria were considered to be noncompliant with the study protocol based on the modified protocol-compliance criteria:

- Overdose of greater than 10% of the recommended bolus or maintenance doses
- No bolus dose received
- Greater than one bolus dose except in patients undergoing dialysis
- Undetermined bolus dose
- No *abnormal* baseline plasma ammonia value for rescue patients (no time limit restriction)
- No baseline plasma ammonia value for prospectively-treated patients (no time limit restriction)
- Incorrect bolus or FIRST maintenance dose administered, defined as more than 10% difference from recommended doses
- Unknown infusion duration or inadequate infusion information for bolus or FIRST maintenance doses
- Unknown UCD diagnosis or diagnosis other than UCD
- Maintenance dose given prior to bolus dose
- Undetermined FIRST maintenance dose

All other patients/episodes were considered compliant with the study protocol based on the modified criteria. Note that patients may have been included in the modified protocol-compliant population even if they received no maintenance dose. Maintenance infusions were not required, per protocol, for patients who were able to tolerate oral medication after the bolus dose, or for patients who were determined not to have UCDs.

6.1.4 Efficacy Findings

Primary endpoint-Survival

The survival rates for all patients and for patients in protocol-compliant and non-compliant groups are listed in Table 1. Survival was greatest (98 to 95%) in the protocol-compliant and modified-protocol-compliant patients, respectively, but this constituted only 13 to 21%, respectively, of the patients enrolled in the study. However the overall survival rate was very similar to the survival rate for protocol and modified protocol- non-compliant patients at approximately 80%.

Table 1					
Patient Death by Treatment Protocol					
Patient Number¹					
Outcome	Total	Protocol-Compliant	Protocol-Non-Compliant	Modified Protocol - Compliant	Modified Protocol-Non-Compliant
Alive	252 (80%)	40 (98%)	236 (79%)	62 (95%)	323 (79%)
Dead	64 (20%)	1 (2%)	63 (21%)	3 (5%)	61 (21%)
Total	316	41	299	65	292
Episode Number					
Alive	981 (94%)	65 (98%)	916 (94%)	122(98%)	860(93%)
Dead	64 (6%)	1 (2%)	63 (6%)	3 (2%)	61 (7%)
Total	1045	66	979	125	920

Data Source Tables 7.4-1 to 7.4-3 from Comprehensive Clinical Report

¹Patient could have multiple episodes thereby they could be counted in both the protocol compliant and noncompliant groups.

The most common reasons for noncompliance with the treatment protocol had to do with inadequate documentation of baseline ammonia levels and/or inadequate infusion information. It is possible that some of the higher mortality in the non-compliant groups could have been due to inadequate dosing or overdosing of Ammonul. In addition, some of the noncompliant patients deviated from the treatment protocol because they received documented additional boluses of Ammonul following a poor response to the first bolus. Patients with severe enzyme deficiencies are more likely to have a poor response to the initial bolus and this could have contributed to a higher mortality rate in these protocol non-compliant patients.

The survival rate for infants under 30 days of age was 70/104=67% compared to 207/237=87% for subjects presenting after 30 days of age. This likely reflects that infants who present within the first week of life are likely to have more severe enzyme deficiencies. Survival rates were lower among patients with unknown diagnoses or non-UCD diagnoses, 62% compared to patients with OTCD 80%, ASD 90%, CPSD 84% and ALD 100%. Survival rates were higher in female patients with OTCD 88%, most of whom probably had late-onset OTCD, compared to male patients with OTCD 71%, who can present with neonatal and infantile-onset OTCD.

AGD and NAGSD are considered the rarest UCDs. There were only two patients with AGD and no patients with NAGSD enrolled in this study. The survival rate for AGD (50%) was lower than that of other forms of UCDs even though AGD typically produces less severe hyperammonemia

than other UCDs. However, given that there were only two patients with AGD, no reasonable estimate of survival associated with Ammonul therapy in these patients can be made based on these results.

There were only two patients with THN enrolled in this study and both survived.

There were only 5 prospectively treated patients. Two of these died, one from a suspected beta-fatty acid oxidation defect and one from an unknown cause.

Secondary endpoint- Neurological status

Of 123 episodes of coma documented on admission, 90% (111/123) had no coma at time of discharge, and only 10% (12/123) either had a coma (n=3) or no documented coma information (n=9) suggesting a general marked improvement following treatment with Ammonul. In six episodes, patients who initially presented without a coma developed coma by the end of treatment, before they were transferred to another hospital (n=4) or died (n=2).

Coma was more common on admission in infants under 30 days of age (48%), compared to older patients (8%). A similar trend was seen at time of discharge although the overall frequency was much less (5% for <30 days of age, <1% for >30 days of age). This likely reflects that infants who present within the first week of life are likely to have more severe enzyme deficiencies.

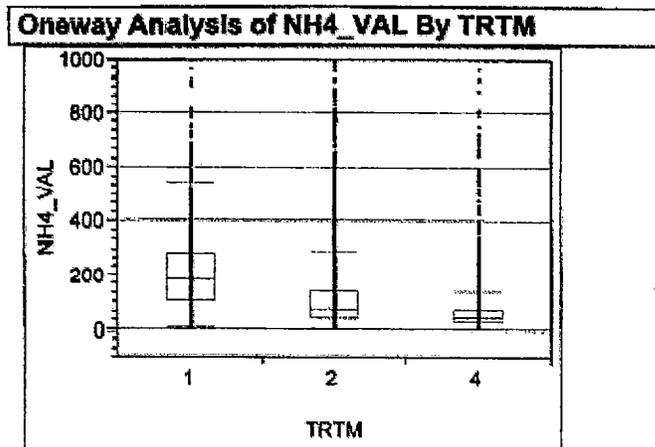
There were no data to confirm improvement in neurological status in the prospectively treated patients.

Secondary endpoint- Plasma ammonia levels

In a historical study describing ammonia levels in 108 hyperammonemic episodes in patients with UCDs (Uchino et al. 1998), there were no observations of severe neurological damage if peak ammonia levels were <5 times ULN (180 μ mol/L). Utilizing this information, the sponsor evaluated the change in plasma ammonia levels associated with Ammonul treatment in patients with initial values >4 times ULN (very high). Of 268 patients whose baseline ammonia levels were > 4 times ULN, 245 or 91% had last measured ammonia levels \leq 4 times ULN, and 151 or 56% had ammonia levels that were \leq 1 times ULN.

An analysis of plasma ammonia levels for all patients shown in Fig. 5 shows a statistically significant decrease in ammonia levels from pretreatment, to infusion and post-infusion.

Fig. 5
Plasma Ammonia Levels in All Patients Before, During and After Treatment with Ammonul¹



¹TRTM=1 Preinfusion, TRTM=2 During Infusion, TRTM=4 Post Last Infusion
P<0.0001 ChiSquare, Data Source DERCHE1A dataset

The mean plasma ammonia level at the last value for infants under 30 days of age was 251 µmol/L (SD=522) compared to 56 µmol/L (SD=93) for subjects presenting after 30 days of age. This likely reflects that infants who present within the first week of life are likely to have more severe enzyme deficiencies. Mean plasma ammonia levels at the last value for patients with the most common UCDs i.e. OTCD, ASD CPSD and ALD, ranged from a low of 38 µmol/L in ALD to a high of 97 µmol/L in CPSD. Patients with unknown diagnoses or non-UCD diagnoses had much higher mean plasma ammonia levels at the last value (221 µmol/L, SD=450) consistent with the lower survival rates seen in these patients. Mean plasma ammonia levels at the last value were lower in female patients with OTCD (58 µmol/L) most of whom probably had late-onset OTCD, compared to male patients with OTCD (87 µmol/L), who can present with neonatal and infantile-onset OTCD, consistent with the difference in survival rates seen between males and females patients with OTCD. Mean plasma ammonia levels at the last value were nearly normal at 48 µmol/L for patients with THN despite the very high baseline plasma ammonia levels seen here (745 µmol/L) and typical of this disorder.

There were no data to confirm improvement in ammonia levels in the prospectively treated patients.

Secondary endpoint- Number and percent of patients requiring dialysis (excluding neonatal rescue patients who were required to receive dialysis as part of the treatment protocol)

Dialysis was recommended in all cases for patients not responding to treatment i.e. no significant decrease in ammonia levels after 8 hours of treatment, in patients who developed hyperammonemic encephalopathy or in patients who showed signs of Ammonul overdose (e.g. obtundation in the absence of hyperammonemia, hyperventilation, severe compensated

Clinical Review

{Insert Reviewer Name}

{Insert Application and Submission Number}

{Insert Product Trade and Generic Name}

metabolic acidosis with a possible respiratory component, large anion gap, hypernatremia and hyperosmolarity, progressive encephalopathy, or cardiovascular collapse). Therefore the need for dialysis, excluding neonatal rescue patients, can be considered a treatment failure. The frequency of dialysis in all patients excluding neonates was low 37/242=15% occurring in 81/944=9% of the episodes. These data suggest that most patients with UCDs who present after 30 days of age can be treated effectively with Ammonul and will not need dialysis.

6.1.5 Clinical Microbiology

No clinical Microbiology data were included in this submission.

6.1.6 Efficacy Conclusions

The survival rate for all patients was 80% with better results in patients with known UCDs such as OTCD 80%, ASD 90%, CPSD 84% and ALD 100% compared to patients with unknown disorders or nonUCDs 62%. This is much improved over historical reports which showed an overall survival rate of 48% after the first hyperammonemic crisis observed in 216 Japanese patients between 1978 and 1995 prior to the development of IV therapy with sodium phenylacetate and sodium benzoate (Uchino et al. 1998).

The survival rate for infants under 30 days of age was 70/104=67% compared to 207/237=87% for subjects presenting after 30 days of age. This is compared to a historical rate of 43% and 75%, respectively, in historical controls (Uchino et al. 1998).

Survival rates were higher in female patients with OTCD (88%), most of whom probably had late-onset OTCD, compared to male patients with OTCD (71%), who may present with neonatal and infantile-onset OTCD. These rates are improved when compared to historical survival rates for neonatal OTCD, late onset disease in females, and males of 14%, 66%, and 59% respectively (Uchino et al. 1998).

Treatment with Ammonul was shown to lower plasma ammonia levels in 91% of patients with baseline values > 4xULN and to improve the neurological status in 96% of patients for whom data were available. Dialysis was necessary to lower plasma ammonia levels in only 15% of all patients excluding neonates, who were required to get dialysis as part of the treatment protocol.

There was no clear evidence for efficacy in the 5 prospectively treated patients.

In summary, Ammonul is effective at lowering plasma ammonia, improving neurological status and limiting the need for dialysis in most patients with UCDs. While some patients with other disorders that cause hyperammonemia were studied and did show some response to therapy, the numbers of these patients were small and there are no good historical controls for comparison. Therefore, continued clinical trials in such conditions are recommended and no recommendation about use of Ammonul for non-UCDs can be made at this time.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

There were 64 deaths among the 316 patients in this study (20%). Most (51/64=80%) were considered not related to study treatment, and 7 (11%) had an unknown relationship to study treatment. Four deaths (6%) were assessed as remotely related to study drug, one death (2%) was considered possibly related (cardiopulmonary arrest due to hyperammonemia), and one death (2%) was considered probably related (increased intracranial pressure due to metabolic acidosis).

For Patient 027.0192, the death was considered remotely related to the primary disease and probably related to the study medication. The cause of death was increased intracranial pressure due to metabolic acidosis. This patient received study medication that exceeded the recommended dose.

For Patient 055.0298, death was considered probably related to the primary disease and possibly related to the study medication. The cause of death was cardiopulmonary arrest due to hyperammonemia.

For the 3 deaths with probable relationship to the primary disease and remote relationship to study drug, the causes of death were cerebral edema (Patient 012.0292), cardiorespiratory failure due to hyperammonemia (Patient 064.0206), and probable sepsis with intractable hypotension (Patient 081.0256, who received a dose of study medication that exceeded the recommended dose).

For Patient 027.0250, death was considered possibly related to the primary disease and remotely related to study medication. The cause of death was fungal sepsis due to an indwelling line catheter.

For Patient 044.0035, the death was considered probably related to the primary disease and of unknown relationship to the study medication. The cause of death was disseminated herpes simplex virus infection.

For 6 patients (9%), the relationship of the death to both the study medication and the primary disease was unknown. The causes of death in these patients were: unspecified (Patients 050.0340, 051.0120, and 060.0338), bowel sepsis (Patient 051.0339), respiratory failure due to hypotension and metabolic acidosis (Patient 059.0113, who received study medication that exceeded the recommended dose), and brain death due to diabetes insipidus, unstable blood pressure, and hyperammonemia (Patient 062.0342).

7.1.2 Other Serious Adverse Events

Serious adverse events (SAEs) were reported in 34% of patients. Serious adverse events were reported most frequently for the following system organ classes: nervous system disorders (16%); metabolism and nutrition disorders (11%); respiratory, thoracic and mediastinal disorders (9%); blood and lymphatic system disorders (7%); and cardiac disorders (5%).

The most frequently reported SAEs were hyperammonemia (5%), brain edema (5%), convulsions (4%), coma (3%), mental impairment (3%), hypotension (3%), metabolic acidosis (3%), and disseminated intravascular coagulation (3%) (see sponsor's Comprehensive Clinical Report (CCR) Table 16).

Potentially treatment-related SAEs (probably or possibly related, or with an unknown relationship) were reported for 16% of patients and in the following system organ classes: nervous system disorders (7%); metabolism and nutrition disorders (5%); respiratory, thoracic and mediastinal disorders (5%); and blood and lymphatic system disorders (3%).

Potentially treatment-related SAEs occurring in > 1% of patients included disseminated intravascular coagulation (2%), metabolic acidosis (2%), brain edema (2%), mental impairment (2%), and hypotension (2%) (see sponsor's CCR Table 16.1).

7.1.3 Dropouts and Other Significant Adverse Events

Adverse events leading to study drug discontinuation occurred in 4% of patients. General disorders and administration-site conditions (injection-site reaction, extravasations, and hemorrhage) and metabolism and nutrition disorders (hyperammonemia, hypoglycemia, and metabolic acidosis) most frequently led to discontinuation (see sponsor's CCR Table 17).

7.1.4 Other Search Strategies

None

7.1.5 Common Adverse Events

There were 163 adverse events in the 316 patients treated with Ammonul (i.e. 52%). The most common adverse events are listed in Table 2.

Table 2	
Adverse Events occurring in $\geq 3\%$ of the Patients Treated with Ammonul¹	
System Organ Class Preferred Term	Patients N=316
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%)

¹Data source sponsor's CCR Table 12

Clinical Review

{Insert Reviewer Name}

{Insert Application and Submission Number}

{Insert Product Trade and Generic Name}

Treatment-related adverse events were reported in 34% of patients. Treatment related adverse events were reported most frequently for the following system organ classes: metabolism and nutrition disorders (14%); nervous system disorders (12%); gastrointestinal disorders (11%); respiratory, thoracic and mediastinal disorders (8%); general disorders and administration site conditions (8%), investigations (8%); and blood and lymphatic system disorders (6%).

The most frequent treatment related AEs were vomiting (8%), hypokalemia (6%), metabolic acidosis (3%), convulsions (3%), mental impairment (3%), anemia (3%), diarrhea (3%), nausea (3%), pyrexia (3%), hyperglycemia (3%), acidosis (2%), hypotension (2%), disseminated intravascular coagulation (2%), hypernatremia (2%), brain edema (2%), headache (2%), agitation (2%), respiratory alkalosis (2%), tachypnea (2%), rash (2%), diaper dermatitis (2%), injection site reaction (2%) (see sponsor's CCR Table 15).

7.1.6 Less Common Adverse Events

Adverse events occurring in <3% of patients but \geq 1% include:

BLOOD AND LYMPHATIC SYSTEM DISORDERS: coagulopathy, pancytopenia, thrombocytopenia

CARDIAC DISORDERS: cardiac arrest, cardio-respiratory arrest, tachycardia

EYE DISORDERS blindness/cortical blindness

GASTROINTESTINAL DISORDERS: abdominal pain, loose stools,

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: injection site edema, injection site pain, lethargy

HEPATOBIILIARY DISORDERS

INFECTIONS AND INFESTATIONS: otitis media, staphylococcal infection

INVESTIGATIONS: aspartate aminotransferase increased, blood culture positive, blood glucose increased, blood urea decreased, hematocrit decreased

METABOLISM AND NUTRITION DISORDERS: hyperchloremia, hypernatremia, hyponatremia, hypophosphatemia

NERVOUS SYSTEM DISORDERS: encephalopathy, headache, intracranial pressure increased

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS: cough, hyperventilation, pulmonary hemorrhage, pulmonary edema, respiratory alkalosis, respiratory failure, tachypnea

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: diaper dermatitis, rash

7.1.7 Laboratory Findings

The mean changes in laboratory values from baseline to last value after treatment (calculated per patient) were less than 10% of the mean baseline value for all lab tests with the exceptions of AST, ALT, plasma glutamine, CO₂ and pO₂. The mean (SD) changes from baseline to last value were -86.4 (951) U/L for AST; -49.9 (895) U/L for ALT, -360 (805) U/L for plasma glutamine, +2.2 (20) mol/L for CO₂, and -9.7 (78) mmHg for pO₂.

Clinical Review

{Insert Reviewer Name}

{Insert Application and Submission Number}

{Insert Product Trade and Generic Name}

Shifts in laboratory test results from a normal value at baseline to an abnormal last value occurred most frequently for pCO₂ (to a low value in 42% of episodes), bicarbonate (to a low value in 35% of episodes), pO₂ (to a high value in 36% and to a low value in 32% of episodes), CO₂ (to a low value in 32% of episodes), glutamine (to a high value in 31% of episodes), glucose (to a high value in 28% of episodes), pH (to a high value in 25% of episodes), and potassium (to a low value in 23% of episodes).

Shifts in individual laboratory test results from normal at baseline to high at last value were observed in $\geq 20\%$ of episodes with available data for the following parameters: serum AST levels in 10 of 51 episodes (20%); serum ALT levels in 11 of 50 episodes (22%); plasma glutamine in 4 of 13 episodes (31%); serum chloride levels in 48 of 244 episodes (20%); serum glucose levels in 53 of 186 episodes (28%); blood pH in 24 of 96 episodes (25%); and pO₂ in 9 of 25 episodes (36%).

Shifts in individual lab test results from normal at baseline to low at last value in $\geq 20\%$ of episodes with data were noted for the following laboratory parameters: serum potassium levels in 73 of 318 episodes (23%); blood CO₂ levels in 67 of 209 episodes (32%); pCO₂ in 23 of 55 episodes (42%); pO₂ in 8 of 25 episodes (32%); and serum bicarbonate levels in 20 of 57 episodes (35%).

Clinically significant laboratory abnormalities were captured as AEs. The most frequently reported laboratory AEs included hypokalemia (3% of episodes), hyperammonemia (2% of episodes), hyperglycemia (2% of episodes), and metabolic acidosis (1% of episodes). The most frequently reported treatment-related laboratory AE was hypokalemia (2% of episodes).

Although this clinical study was initially designed to include prospectively treated patients who were considered at risk for hyperammonemia but did not have hyperammonemia at initial treatment, only 5 such patients were enrolled in this study. Adverse events were attributed to the bolus dose in 2 prospective-treatment episodes and to the maintenance dose in 2 prospective-treatment episodes. Adverse events attributed to the bolus dose in prospective-treatment episodes included increased anion gap, increased AST, increased bilirubin, increased blood glucose, cardiac murmur, abnormal liver function test, decreased total protein, hyperammonemia, hyponatremia, hypokalemia, and respiratory alkalosis. Adverse events attributed to the maintenance dose in prospective-treatment episodes included diarrhea, vomiting, death not otherwise specified, increased conjugated bilirubin, increased bilirubin, decreased blood glucose, decreased blood urea, hyperammonemia, hyperchloremia, hyperkalemia, hyperphosphatemia, hypocalcemia, and diaper dermatitis. Of the two of these patients that died neither was eventually diagnosed with a UCD.

7.1.8 Vital Signs

Vital signs were not collected in this study.

7.1.9 Electrocardiograms (ECGs)

ECGs were not collected in this study.

7.1.10 Immunogenicity

No information regarding immunogenicity was included in this submission. The sponsor did reference several literature reports that sodium benzoate had been reported to impair lymphocyte mitogenesis (Tremblay G.C. and Qureshi I. A.) and decreased superoxide anion and lysozyme release from polymorphonuclear leukocytes (Johansen K.S. and Berger E.M 1983).

7.1.11 Human Carcinogenicity

No information regarding human carcinogenicity was included in this submission. The sponsor did reference several literature reports that there was no demonstrated evidence of carcinogenicity following chronic administration of sodium benzoate to rats (Sodemoto Y. and Enomoto M. 1980) and mice (Toth B. 1984).

7.1.12 Special Safety Studies

No special safety studies were included in this submission.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No information regarding withdrawal phenomena and or abuse potential was included in this submission.

7.1.14 Human Reproduction and Pregnancy Data

Pregnancy Category C labeling is recommended. Animal reproduction studies have not been conducted, and it is not known whether Ammonul can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. However, category C labeling is recommended as the benefits of treating hyperammonemia in a pregnant patient with UCD may outweigh the risks of drug therapy.

7.1.15 Assessment of Effect on Growth

Not applicable.

7.1.16 Overdose Experience

Some patients received more than one bolus and/or more than the recommended dose specified in the protocol (see Section 8.1). In 16 of the 64 deaths, the patient received a known overdose

Clinical Review

{Insert Reviewer Name}

{Insert Application and Submission Number}

{Insert Product Trade and Generic Name}

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

In case of overdose, AMMONUL can be removed by hemodialysis (procedure of choice) or peritoneal dialysis (when hemodialysis is unavailable).

7.1.17 Postmarketing Experience

Not applicable.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

This is an open-label, uncontrolled study in patients with acute hyperammonemia due to UCDs and in neonates potentially at risk for UCDs. A small subgroup of patients with hyperammonemia due to nonUCD causes was also included in the trial.

Patients with UCDs included:

- carbamyl phosphate synthetase deficiency (CPSD)
- argininosuccinate synthetase deficiency (ASD or ASSD)
- ornithine transcarbamylase deficiency (OTCD)
- argininosuccinate lyase deficiency (ASLD)
- arginase deficiency (AGD or ARD)

Patients with nonUCDs included:

- Transient hyperammonemia of the newborn (THN)
- hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome
- carnitine translocase deficiency
- HMG CoA lyase deficiency
- nonketotic hyperglycinemia
- valproic acid induced hyperammonemia
- fatty acid oxidation deficiency

- liver disease
- acidemia

7.2.1.2 Demographics

Similar percentages of male and female patients were present in the total study population. Most patients were under 2 years of age, see Table 3.

		Patients N=316
Gender	Male	158 (51%) ¹
	Female	150 (49%)
	Missing	8
Age (years)	N	310
	Mean (SD)	6.2 (8.54)
	Min–Max	0.0–53.0
Age groups	0–30 days	104 (34%) ¹
	31 days–2 years	55 (18%)
	> 2–12 years	90 (29%)
	> 12–16 years	30 (10%)
	> 16 years	31 (10%)
	Missing	6

¹Missing information was not included in calculation of percentages

The demographics of patients by enzyme deficiencies are listed in Table 4.

		CPSD Patients N=38 (12%)	OTCD Patients N=146 (46%)	ALD Patients N=7 (2%)	ASD Patients N=71 (22%)	AGD Patients N=2 (<1%)	THN Patients N=2 (<1%)	OTHER Patients N=56 (18%)
Gender	Male	18 (50%)	69 (48%)	3 (43%)	35 (50%)	1 (50%)	1 (50%)	33 (61%)
	Female	18 (50%)	74 (52%)	4 (57%)	35 (50%)	1 (50%)	1 (50%)	21 (39%)
	Missing	2	3	0	1	0	0	2
Age (years) ¹	N	37	143	7	70	2	2	55
	Mean (SD)	6.5 (9.65)	7.3 (8.52)	2.9 (5.40)	4.9 (6.10)	9.5(13.44)	0.0 (0.00)	5.7(10.41)
	Min–Max	0.0–38.0	0.0–53.0	0.0–14.0	0.0–27.0	0.0–19.0	0.0–0.0	0.0–51.0
Age groups ¹	0–30 days	10 (27%)	35 (24%)	5 (71%)	26 (37%)	1 (50%)	2 (100%)	26 (47%)
	31 days–2 years	11 (30%)	26 (17%)	0	10 (14%)	0	0	11 (20%)
	> 2–12 years	7 (19%)	55 (37%)	1 (14%)	23 (33%)	0	0	6 (11%)
	> 12–16 years	4 (11%)	14 (10%)	1 (14%)	6 (9%)	0	0	7 (13%)
	> 16 years	5 (14%)	16 (11%)	0	5 (7%)	1 (50%)	0	5 (9%)
	Missing	1	3	0	1	0	0	1

¹For patients with multiple episodes the age refers to the initial presentation

7.2.1.3 Extent of exposure (dose/duration)

The mean (SD) number of episodes per patient was 3.3 (6.2) and ranged from 1 to 77. Of the 316 patients, 185 (59%) experienced 1 episode, 48 (15%) had 2 episodes, and 30 (10%) had 3 or 4 episodes, and 53 (17%) had 5 or more episodes.

The mean length of hospitalization per episode was 9.4 (13) days and ranged from 1 to 171 days. The mean length of hospitalization for patients, summed across all episodes, was 30.5 (46) days. For most episodes (76%), patients were hospitalized for fewer than 10 days.

For 577 of 1045 episodes (63%), patients received one bolus infusion followed by maintenance infusions, as specified in the protocol. For 175 episodes (19%), patients were given maintenance infusions only; for 109 episodes (12%), patients were given multiple boluses and multiple infusions; for 21 episodes (2%), patients were given one bolus and no maintenance infusion; and for 6 episodes (< 1%), patients were given multiple boluses but no maintenance infusion. It should be noted that in some cases, these dosing variations were not deviations from the protocol or from accepted medical practice. Maintenance infusions were not required, per protocol, for patients who were able to tolerate oral medication after the bolus dose, or for patients who were determined not to have UCDs. According to the consensus statement prepared by the UCD Conference Group, multiple bolus doses are acceptable for neonates undergoing dialysis. In 82% of the 738 episodes with available data, the patient was given one bolus dose. Two boluses were reported for 13% of episodes, 3 boluses were reported for 3% of episodes, and 4 or more boluses were reported for 3% of episodes. The mean (SD) durations of treatments were 4.6 (6) days per episode, and 15.0 (26) days per patient (summed across all episodes). The most frequent treatment duration was 10 days or fewer, reported for 92% of episodes and for 68% of patients (summed across all episodes).

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

None.

7.2.3 Adequacy of Overall Clinical Experience

There were 316 patients treated in 1,045 episodes in the original submission with an additional 106 episodes included in the 4-month safety update for this orphan indication. While randomized double blind trials provide the most clear efficacy and safety data, such a trial in this patient population would have been unethical. Comparison to historical controls was adequate to confirm the clinical benefit of this drug.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No special animal or *in vitro* testing was submitted.

7.2.5 Adequacy of Routine Clinical Testing

All patients treated with Ammonul were hospitalized and under the care of physicians with intensive care training. Blood samples were collected for measurement of amino acid levels, clinical chemistry, ammonia, blood pH and pCO₂. Patients were monitored closely for changes in respiratory, hemodynamic, hematological, metabolic and neurological status.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The enzymatic pathways for metabolism of phenylacetate and benzoate are well described in the literature (Brusilow and Horwich). No drug-drug interaction or CYP450 studies were included in this submission.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

There were an insufficient number of patients with hepatic or renal insufficiency in this clinical study to determine the safety and efficacy of Ammonul in such patients. A patient registry to follow such patients is recommended.

There is insufficient information to determine if Ammonul may cause fetal harm if given to pregnant women. A patient registry to follow pregnancy outcomes for women treated with Ammonul during pregnancy is recommended.

7.2.8 Assessment of Quality and Completeness of Data

The general quality of the data submitted for review was adequate to make a clear assessment of risk versus benefit.

7.2.9 Additional Submissions, Including Safety Update

The 4-month safety update includes data from case reports received by the sponsor between June 01, 2003 and August 31, 2004. These data from 106 new episodes corresponded to only about 10% of the previous exposures (1045 episodes) so the sponsor was not required to perform a reanalysis of the total exposure.

The demographics show that the patient population in the safety update included a higher percentage of older patients between the ages of 16 to 55 and infants under 30 days of age in contrast to the original submission (see Table 5).

Table 5			
Demographics for All Episodes			
		Original Submission	4-month SUR
Episodes		N=1045	N=106
Gender	Male	458 (44%)	41 (39%)
	Female	576 (56%)	64 (61%)
	Missing	11	1
Age (years)	N	1038	106
	Mean (SD)	8.5 (7.44)	11.3 (10.2)
	Median	7.0	14.5
	Min–Max	0.0–53.0	0.0–55.0
Age groups	0–30 days	106 (10%)	18 (17%)
	31 days–2 years	189 (18%)	12 (11%)
	> 2–12 years	421 (41%)	21 (20%)
	> 12–16 years	154 (15%)	12 (11%)
	> 16 years	168 (16%)	43 (41%)
	Missing	7	0

Data Source PSUR Table 5.1-1 and CCR Table 6.2-1

Among enzyme-deficiency subgroups, there were 33 new OTCD episodes (551 old episodes), 22 new ASD episodes (260 old episodes), 31 new CPSD episodes (154 old episodes), 1 new ALD episode (9 old episodes), 2 new THN episodes (2 old episodes), and 17 new “other” episodes (64 old episodes). There were no new AGD episodes. Most episodes in the safety update were for rescue treatment. There were only two new cases of prospective treatment.

There were 9 deaths among the 106 episodes (8%) similar to the mortality rate seen in the initial submission (64/1045 episodes=6%). Most (6) were considered not related to study treatment [cerebral edema secondary to hyperammonia (2), hyperammonia (1), respiratory failure (1), valproate toxicity/sepsis/ARDS (1), and ARF/isovaleric academia (1)]. One death was considered possibly related to study drug (cardiac arrest due to subtentorial brain herniation and cerebral edema; this patient received 120% of the recommended dose during maintenance infusion), and for 2 deaths, the relationship to study drug was unknown (withdrawal of life support due to persistent hyperammonemia/lactic acidosis, and cause of death unspecified/fungal organism seen in lung and spleen at autopsy; both patients received higher than the recommended maintenance infusion, 250% and 190% respectively), source Listing 16 PSUR.

The survival rate by enzyme deficiency, calculated per total episodes, was similar or better than observed in the original submission for most UCDs i.e. (30/33) 91% for OTCD, (22/22) 100% for ASD, (31/31) 100% for CPSD and (1/1) 100% for ALD. The survival rate was lower for THN (1/2) 50% in the safety update compared to (2/2) 100% in the original submission. The survival rate was lower for patients in the “other” group compared to patients with UCDs, 71% and 92% respectively, but this was similar to the rate of 68% seen in “other” patients in the original submission.

Serious adverse events (SAEs) occurred in 20 episodes. The SAEs reported in more than one episode were convulsions (4), brain edema (3) and hypotension (2). Potentially treatment-related

SAEs were reported in 3 patients. No treatment-related SAE was reported in more than one episode (source Listing 20 PSUR).

Adverse events leading to study drug discontinuation were reported in 4 episodes (injection site reaction, metabolic acidosis, hyperammonia, and mental status changes/hemodynamic instability, source Listing 21 PSUR).

Adverse events were observed in 29 episodes (27%). Adverse events were reported most frequently in the following system organ classes: psychiatric disorders 11 episodes (10%), nervous system disorders 10 episodes (9%), metabolism and nutrition disorders 5 episodes (5%), and cardiac disorders 5 episodes (5%). Most AEs were reported in only 1 episode. The most frequently reported AE was aggression (4 episodes, 4%). Tachycardia and agitation were each reported in 3 episodes (3%). Abdominal pain, metabolic acidosis, back pain, convulsions, mental status changes, hypertension and hypotension were each reported in 2 episodes (2%), source table 6.2-1 PSUR. There were no AEs during the 2 prospective-treatment episodes. In general the adverse event profile was similar to what had been observed in the original submission.

Treatment-related AEs were reported in 17 episodes (16%). Treatment-related AEs were reported most frequently among the following body systems: psychiatric disorders 9 episodes (8%), nervous system disorders 4 episodes (4%), and cardiac disorders 4 episodes (4%). Most treatment-related AEs were reported in only 1 episode. Treatment-related tachycardia and aggression were each reported in 3 episodes (3%), and treatment-related abdominal pain, metabolic acidosis, agitation, and mental status changes were each reported in 2 episodes (2%), source Table 6.2-3 PSUR.

Among the most frequent diagnoses, the incidence of AEs was greatest among episodes in patients with CPSD (45%). Among CPSD episodes, AEs were reported most frequently in the following body systems: psychiatric disorders (26%) including aggression (13%), cardiac disorders (10%) including tachycardia (10%), and gastrointestinal disorders (10%); all were more frequent among CPSD episodes than in any other enzyme-deficiency subgroup. Injection site disorders were reported in 9% of patients with ASD and were not reported with other UCDs (source Table 6.2-3 PSUR).

The percentage of episodes with shifts from coma at admission to no coma at discharge was 100% among OTCD, ASD, ALD, and THN episodes, and was 50% among "other" episodes (Source Table 8.4.2 PSUR). No patient with CPSD was comatose at admission. Thus, all episodes in which the patient was not revived from coma occurred in the "other" diagnoses subgroup. Shifts from no coma at admission to coma at discharge occurred in 1 ASD episode and 1 CPSD episode.

In 40 of 44 episodes (91%), there were shifts from baseline ammonia levels > 4xULN (very high) to levels ≤ 4xULN (high) at the last value prior to discharge (source Table 7.1-2 PSUR). Ammonia levels remained at levels > 4xULN in only 3 of 44 episodes (7%). Data was missing in one patient (2%).

Changes in mean lab values from baseline to last value after treatment (calculated per patient) were less than 10% of the mean value except for AST, ALT, plasma glutamine, glucose and pO₂. Mean changes from baseline to last value were 11% for AST, 300% for ALT, -45% for glutamine, +12% for glucose and -31% for pO₂ (source Table 7.2.1 PSUR). The large mean change from baseline in ALT was chiefly due to a large increase (3853 U/L) in a single patient; the median change was -2.5 U/L.

In summary, the general adverse event profile for patients with UCDs in the safety update was similar to what had been observed in the original submission. No new SAEs or AEs leading to discontinuation were observed.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Common adverse events, serious adverse events (SAEs) and treatment-related adverse events were reported in 52, 34 and 34% of patients, respectively.

The following adverse events were observed in clinical trials and can be treatment related.

- Gastrointestinal disorders- Nausea, vomiting and diarrhea were more common in children over 30 days of life. The label should mention that anti-emetic agents may be needed during the Ammonul infusion.
- Injection site disorders- Injection site edema, erythema and hemorrhage were observed in the clinical study. The label should state that Ammonul should be infused through a central line to avoid peripheral extravasations and that the drug product requires adequate dilution prior to IV administration.
- Fluid overload- Ammonul contains a large amount of sodium and must be infused at relatively high bolus infusion rates. The label should mention the need to monitor serum sodium levels and fluid status especially in patients with cardiac failure or renal insufficiency.
- Cerebral edema- Increased intracranial pressure and cerebral edema can be due to hyperammonemia or a consequence of Ammonul overdose. Patients' neurological exams need to be monitored carefully during Ammonul infusion. These patients are at increased risk of seizures and mental status changes which were observed more commonly in patients with OTCD and CPSD.
- Electrolyte abnormalities- Hypokalemia, hyperglycemia, acidosis have been observed in clinical trials and can be related to drug therapy. The infusion solution is diluted with a large amount of D10W. Urine potassium loss occurs due to excretion of the drug metabolites. Arginine therapy has been associated with hyperchloremic acidosis. Frequent chemistry profiles, blood pH and pCO₂ monitoring is recommended.

- Hemodynamic status- Patients are at risk for both hypertension and hypotension as a result of fluid and electrolyte disturbances and pre-existing cardiac or renal disease. Patients should be monitored in an intensive care setting during IV Ammonul infusion.
- Blood system disorders- Patients treated with Ammonul were seen at increased risk of coagulopathy, thrombocytopenia, anemia and disseminated intravascular coagulation. This may be related to the primary underlying disorder, sepsis or liver failure and not directly related to the drug product.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Only one study was included in this submission.

7.4.2 Explorations for Predictive Factors*

Adverse events were somewhat more frequent among patients ≤ 30 days of age, compared with patients > 30 days of age. Adverse events were reported for 56% of episodes and 57% of patients among the patients ≤ 30 days of age, and 28% of episodes and 47% of patients among the patients > 30 days of age. Blood, lymphatic system disorders and vascular disorders (specifically hypotension, 11% of patients) were more frequent among patients ≤ 30 days of age, while gastrointestinal disorders (specifically vomiting, diarrhea and nausea at 11, 4 and 3% of patients, respectively) were more frequent among patients ≥ 30 days of age.

Nervous system disorders were somewhat more frequent in patients with OTCD and CPSD, compared with patients with ASD and patients with “other” diagnoses. None were reported for patients with ALD or AGD. Convulsions and mental impairment were reported primarily in patients with OTCD (10 and 11 patients, respectively) and CPSD (5 and 4 patients, respectively).

Adverse events that were more common in patients receiving greater than the recommended bolus were anion gap increased (3 vs. 1%), hyperammonemia (4 vs. 1%), hyperglycemia (4 vs. 1%), hypokalemia (4 vs. 2%), metabolic acidosis (3 vs. 1%), headache (3 vs. 0%), and mental impairment (4 vs. 1%). Somewhat unexpectedly, vomiting was slightly more common in patients receiving less than or equal to the recommended dose (7% vs. 5%).

7.4.3 Causality Determination

Neurotoxicity was reported in cancer patients receiving intravenous phenylacetate, 250-300 mg/kg/day for 14 days, repeated at 4-week intervals. Manifestations were predominantly somnolence, fatigue, and lightheadedness, with less frequent headaches,

dysgeusia, hypoacusis, disorientation, impaired memory, and exacerbation of a pre-existing neuropathy. The acute onset of symptoms upon initiation of treatment and reversibility of symptoms when the phenylacetate was discontinued suggest a drug effect (Thibault A. et al. 1994 and 1995). Consistent with the results reported in the literature, headache and mental impairment were also more common in patients treated with higher than the recommended bolus dose in this clinical protocol suggesting causality.

The fluid and electrolyte problems which were also more frequent in patients treated with higher than the recommended dose need not be attributed to Ammonul, but may also be due to a higher than recommended dose of D10W or arginine.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Ammonul is an IV medication. The recommended dose is 250 mg/kg (5.5g/m²) IV bolus over 90 to 120 min followed by maintenance therapy with the same dose over 24 hours. Multiple boluses can be given to neonates undergoing dialysis. A summary of Ammonul dosing in this clinical trial is given in Table 6.

	Episodes N=1045	Patients N=316
Treatment description		
One bolus dose then maintenance infusion	577 (63%)	
One bolus only; no maintenance infusion	21 (2%)	
Bolus not given; maintenance infusion only	175 (19%)	
Multiple boluses; no maintenance infusion	6 (1%)	
Multiple boluses; multiple infusions	109 (12%)	
Other	25 (3%)	
Missing	132	
Duration of treatment (days) ¹		
N	1015	314
Mean (SD)	4.6 (6.45)	15.0 (25.83)
Median	3.0	7.0
Min-Max	1.0-72.0	1.0-300.0
0-10 days	931 (92%)	214 (68%)
11-20 days	56 (6%)	35 (11%)
21-50 days	23 (2%)	47 (15%)
51-100 days	5 (1%)	14 (4%)
>100 days	0	4(2%)
Missing	30	2

Clinical Review

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Table 6

Summary of Ammonul Dosing for All Episodes

	Episodes N=1045	Patients N=316
sodium phenylacetate/sodium benzoate bolus dose (mg/kg) ^{2,3}		
N	638	
Mean (SD)	700 (944)	
Median	200	
Min-Max	0-236,000	
sodium phenylacetate/sodium benzoate bolus dose (g/m ²) ^{3,4}		
N	330	
Mean (SD)	24.4 (324.63)	
Median	5.6	
Min-Max	0.4-5902.8	
<p>¹ For each episode, the duration of treatment was calculated as the last sodium phenylacetate/sodium benzoate dose date minus the first sodium phenylacetate/sodium benzoate dose date + 1. For the summary of patients, the duration of treatment was combined across all episodes.</p> <p>² Bolus dose (g/kg) was calculated as grams of sodium phenylacetate/sodium benzoate divided by the patient's weight in kilograms.</p> <p>³ Each bolus dose was considered separately in this summary. That is, if a patient received more than one bolus dose in the same episode, each dose was included in the summary. Therefore, the total number of doses may be larger than the total number of episodes.</p> <p>⁴ Bolus dose (g/m²) is calculated as grams of sodium phenylacetate/sodium benzoate divided by the patient's body surface area.</p> <p>Source: Table 8.1-1 Comprehensive Clinical Report</p>		

8.2 Drug-Drug Interactions

The following medications could interfere with treatment and should be avoided:

- antibiotics such as penicillin could affect the overall disposition of the infused drug
- probenecid, may affect renal excretion of phenylacetylglutamine and hippurate
- corticosteroids, may cause breakdown of body protein and could potentially increase ammonia levels
- valproic acid and haloperidol have been reported to induce hyperammonemia

8.3 Special Populations

non-UCDs- While a small number of patients with hyperammonemia due to non-UCDs were studied and did show some response to therapy, the number of these patients was too small to draw clear conclusions about efficacy. Additionally, there are no good historical controls for comparison. Therefore, continued clinical trials in such conditions are recommended and no recommendation about use of Ammonul in patients with non-UCDs can be made at this time.

Renal Failure-There were five patients identified with renal insufficiency upon admission to the study. Hemodialysis was employed in two of the five patients but both of these patients died. For effective Ammonul drug therapy, renal clearance of the drug metabolites and subsequently ammonia is required. Therefore, patients with impaired renal function should be closely monitored.

Liver Failure- Limited information is available on the metabolism and excretion of sodium phenylacetate and sodium benzoate in patients with impaired hepatic function. Since metabolic conjugation of sodium phenylacetate and sodium benzoate is known to take place in the liver, care should be used in administering Ammonul to patients with hepatic insufficiency.

8.4 Pediatrics

This drug was studied in pediatric patients including patients in the early neonatal period.

8.5 Advisory Committee Meeting

None.

8.6 Literature Review

See Introduction and Background, Section 2.

8.7 Postmarketing Risk Management Plan

None.

8.8 Other Relevant Materials

None.

9 OVERALL ASSESSMENT

9.1 Conclusions

- Ammonul is effective at improving survival, lowering plasma ammonia levels, improving neurological status and limiting the need for dialysis in most UCD patients during episodes of acute hyperammonemia.
- Patients treated with Ammonul must be monitored closely for electrolyte abnormalities, fluid overdose, changes in hemodynamic status, cerebral edema, injections site reactions, gastrointestinal disturbances and hematological disorders.

- There are insufficient data to support treatment of acute hyperammonemia with Ammonul in patients with non-UCDs or to recommend prospective treatment of neonates with normal plasma ammonia levels but suspected of having a UCD.

9.2 Recommendation on Regulatory Action

An approval action is recommended.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

None.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

- Patient registry to follow off-label use of Ammonul in patients with non-Urea Cycle Disorders.
- Patient registry to follow safety and efficacy in patients with hepatic or renal insufficiency.
- Patient registry to follow pregnancy outcomes for women treated with Ammonul during pregnancy.

9.4 Labeling Review

This medical officer recommends the following changes to the original label submitted by the sponsor. The most current revised label negotiated between the Division and the sponsor is located in the appendix section 10.2. The final approved label will be included in the approval letter.

Medical Officer's comments:

CLINICAL PHARMACOLOGY-

The sponsor should include information describing the clinical presentation and diagnosis of the common UCDs.

19 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

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Recommend approval of application. Please see team leader memo
for additional comments.