CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-562

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	March 16, 2010
From	Lynne Yao, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 022562
Applicant	Orphan Europe
Date of Submission	June 17, 2009
PDUFA Goal Date	March 18, 2010
Proprietary Name / Established (USAN) names	Carbaglu/Carglumic acid
Dosage forms / Strength	200 mg tablet
Proposed Indication(s)	1. Adjunctive therapy in pediatric and adult patients for the treatment of acute hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS). 2. Maintenance therapy in pediatric and adult patients for chronic hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS).
Recommended:	*Approval*

1. Introduction

This New Drug Application (NDA) is for a new molecular entity, Carbaglu (USAN: carglumic acid), which is a structural analogue of N-acetylglutamate (NAG), an allosteric activator of carbamyl phosphate synthetase (CPS), the first enzyme in the urea cycle. Carbaglu is intended to treat patients with hyperammonemia due to N-acetyl glutamate synthase (NAGS) deficiency. The product is to be administered orally, 2-4 times daily before meals, at an initial dose of 100-250 mg/kg of body weight. The Applicant proposed the following indication for Carbaglu:

> *"Carbaglu® (carglumic acid for oral use) is indicated for the specific treatment of hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS deficiency)"*

The NDA relies upon a single, retrospective review of the clinical course of 23 patients with NAGS deficiency treated with Carbaglu over a 21 year period. The Applicant also included data from a three-day open-label study in 3 patients with NAGS deficiency treated with Carbaglu. Issues relating to the quality and quantity of the data presented in this application will be discussed in further detail in this memo.

Although the data submitted in support of the efficacy of Carbaglu in the treatment of hyperammonemia due to NAGS deficiency were limited and retrospectively obtained, the data appear to represent a substantial number of patients with NAGS deficiency given the extreme rarity of the condition (estimated 25-50 patients known worldwide). Additionally, the data support the short and long-term effectiveness of Carbaglu in treatment of hyperammonemia based on the rapid and sustained normalization of plasma ammonia levels in all NAGS deficiency patients for whom data were available. However, due to the severely limited data in patients who did not receive any other concomitant ammonia lower therapies, Carbaglu should be considered as an *adjunctive* treatment for acute hyperammonemia in patients with NAGS deficiency. Furthermore, clear recommendations regarding maintenance dosing of Carbaglu must be determined based on careful monitoring of plasma ammonia levels because insufficient data were available to determine a standard, maintenance dose or dosing regimen.

The safety database for Carbaglu includes 23 NAGS deficiency patients treated with Carbaglu for up to 21 years. The majority of patients 14/23 were treated with Carbaglu for at least 5 years. There were 2 patient deaths that were assessed as not related to treatment with Carbaglu and 10 patients who developed serious adverse events that were assessed as not related to treatment. Many of the serious adverse events reported appear to be related to the patient's underlying disease. Thus, the safety profile of Carbaglu appears reasonable based on the small number of deaths, serious adverse events, and significant adverse events reported. Nevertheless, the retrospective nature of the safety data collected, and the lack of systematic and prospective plan for reporting of adverse events precludes the ability to make clear conclusions regarding the long-term safety of Carbaglu.

Additionally, the long-term safety of Carbaglu has not yet been established because of nonclinical and clinical concerns that will be addressed in this memo. The pharmacotoxicology and clinical reviewers recommend additional postmarketing requirement studies to establish the long-term safety of Carbaglu. These studies have been fully negotiated with the Applicant. The Applicant has agreed to perform a two-year carcinogenicity study in a single species. Additionally, the Applicant has agreed to develop a registry for NAGS deficiency patients that will evaluate long-term safety. As a sub-study of this patient registry, the Applicant has also agreed to collect information on pregnancy and fetal outcomes in patients who have received Carbaglu.

There were two post-marketing commitment studies that were also negotiated with the Applicant during the review cycle. These post-marketing commitments were recommended by the Office of Clinical Pharmacology after review of the clinical pharmacology information submitted in support of the NDA. The data submitted did not specifically address the potential for carglumic acid to produce drug-drug interactions. Therefore, the post-marketing commitments studies plan to evaluate the effect of carglumic acid on cytochrome P450 enzymes.

Additionally, the Agency requested that the Applicant provide a valid National Drug Code (NDC) number, approved bar code, and name of drug product distributor, if any, to complete carton, container, and label reviews. The Applicant informed the Agency that an NDC number request and bar code exemption request were submitted to the Agency late in the review cycle. The Office of New Drug Quality Assessment (ONDQA) reviewed these issues and agreed that an approval action could still be taken if the following conditions were agreed upon with the Applicant:

1. Once the NDC numbers have been assigned by FDA, these will be added to the package insert and the carton/container labeling.
2. If the request for exemption from the requirement of using a bar code is denied by FDA, a bar code will be added to the label.

Finally, deficiencies that were noted during inspection of the drug product manufacturing facility, (b) (4) led to the issuance of a Form 483 in November, 2009. The Office of Compliance recently reviewed final responses from (b) (4) and determined that the responses to the deficiencies were satisfactory. Therefore, on March 15, 2010, the Office of Compliance issued an "Acceptable" rating for the drug product manufacturing facility.

The following review disciplines have provided written evaluations and recommendations that were reviewed as part of this document:

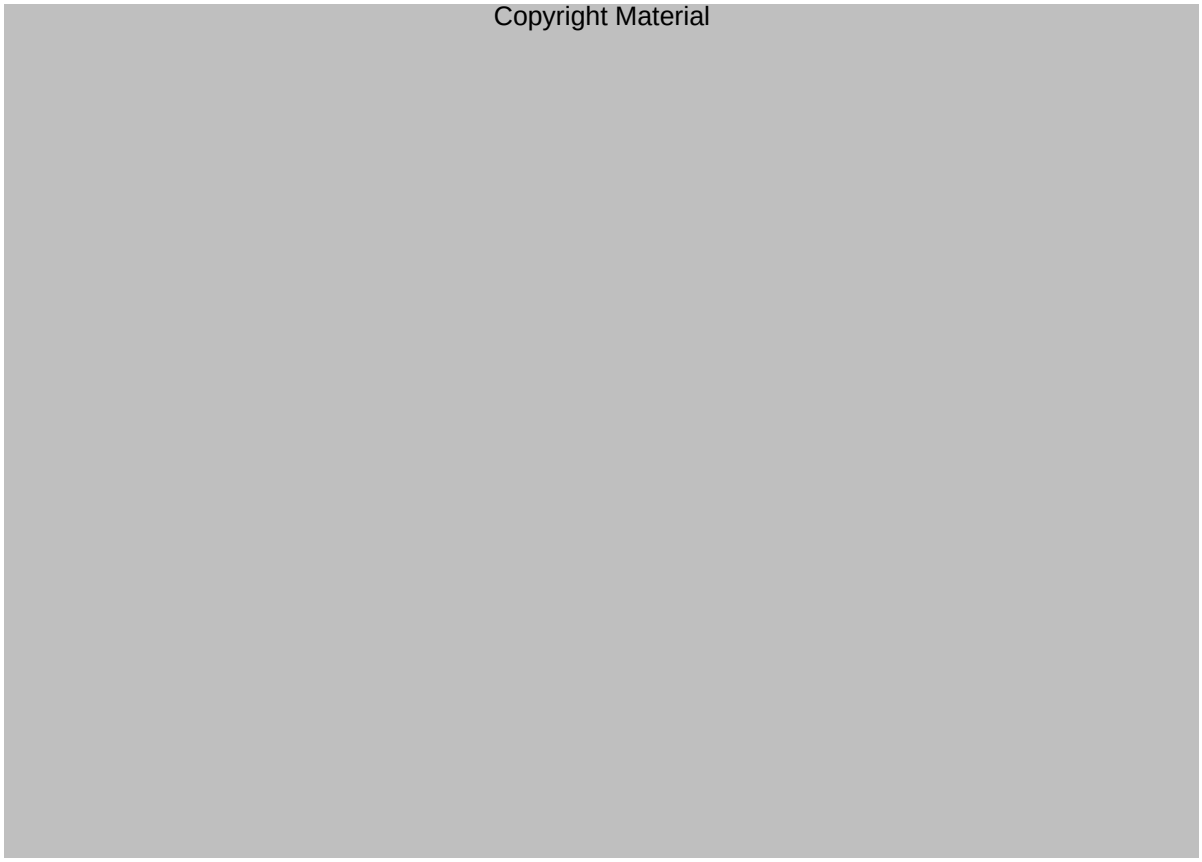
Clinical Review by H. Sile and V. Elgin, dated February 18, 2010
Chemistry Review by M. Haber, Division of Premarketing Assessment I, Office of New Drug Quality Assessment (ONDQA), with concurrence by M.J. Rhee, dated February 23, 2010
Pharmacology/Toxicology Review by Y.C. Ng, dated February 24, 2010

Supervisory Pharmacology Memo by D. Joseph dated March 11, 2010
Clinical Pharmacology Review by K. Estes, dated February 24, 2010
Division of Medication Error Prevention and Analysis (DMEPA), Proprietary Name, Label and Labeling Review by Z. Oleszczuk, dated February 25, 2010
Division of Drug Marketing, Advertising, and Communications (DDMAC), Product Labeling review by K. Klemm, dated March 3, 2010
Memo, CDER Office of Compliance, Division of Manufacturing and Product Quality, dated March 15, 2010
Division of Scientific Investigations (DSI) review by K.W. Malek, dated December 4, 2009 with addendum by A. Dasgupta dated March 5, 2010
Pediatric and Maternal Health Staff (PMHS), Product Labeling review by J. Best, dated March 3, 2010

The reviews should be consulted for more specific details of the application. This memorandum summarizes selected information from the review documents.

2. Background

Clinical Background
The urea cycle is the final common pathway for the excretion of waste nitrogen in mammals and consists of 6 enzymes: (*N*-acetyl-glutamate synthetase, carbamyl phosphate synthetase [CPS], ornithine transcarbamylase [OTC], argininosuccinate synthetase [AS], argininosuccinate lyase [AL], and arginase) (see Figure 1).



Urea cycle disorders result from a deficiency of any of the enzymes involved in the urea cycle. These disorders are autosomal recessive diseases with the exception of ornithine transcarbamylase deficiency, which is an X-linked disorder. Urea cycle disorders have an overall prevalence of approximately 1 in 30,000 live births. OTC deficiency is the most common urea cycle disorder, while NAGS deficiency is presumed to be one of the rarest. The exact incidence of NAGS deficiency is unknown because patients with NAGS deficiency are often not clinically distinguishable from patients with CPS deficiency. However, there have only been approximately 50 known cases reported in the literature worldwide to date.

NAGS deficiency is a rare urea cycle disorder which results from a defect in N-acetylglutamate synthetase. Inherited NAGS deficiency results from one or more mutations in the NAGS gene, which causes an absence or a decrease in the enzyme activity. Without the co-factor NAG, CPS is catalytically inactive. The gene for NAGS is located on the long arm of chromosome 17 within band 17 q21.31, and the molecular diagnostic methods became available in 2003.

NAGS deficiency may present throughout life, but the disease is generally divided into two types; neonatal-onset and late-onset, and correlates with degree of NAGS deficiency. The neonatal-onset disease is associated with complete absence of NAGS activity and is generally more severe than later-onset. Neonatal-onset NAGS deficiency patients may present with respiratory alkalosis, hypotonia, lethargy, and vomiting, and symptoms can progress to cerebral edema, seizures, and death. If patients survive an acute hyperammonemic episode in the newborn period, significant sequelae can result (e.g., development delays, permanent neurocognitive impairment and seizure disorder). Neurologic outcome in patients with neonatal-onset urea cycle disorders is generally poor. One study reported that 79% of children who presented with neonatal hyperammonemic coma had one or more developmental disabilities at 12-74 months of age and a mean IQ of 43±6.[1]

Late-onset NAGS deficiency has a variable age of onset, and the degree of NAGS enzyme activity is widely variable. Patients with late-onset disease may present from the first year of life to adulthood. Symptoms result primarily from hyperammonemia, and the most common clinical findings include central nervous system symptoms such as lethargy, irritability, or somnolence. These symptoms may progress to agitation, disorientation, combativeness, ataxia, and amblyopia. Children with partial enzymatic defects tend to have better outcomes than the ones with complete absence of NAGS activity. Children with partial NAGS deficiency may exhibit cognitive dysfunction such as learning disabilities and attention deficit hyperactivity disorders.

The diagnosis can be established by genetic testing. Additionally, laboratory findings associated with NAGS deficiency include elevated plasma ammonia level, elevated plasma glutamine, normal or low levels of plasma citrulline, normal urinary orotic acid and normal pH or respiratory alkalosis. However, clinical symptomatology and

1 Msall M, Batshaw M, Suss R, et al. Neurologic outcome in children with inborn errors of urea synthesis: outcome of urea-cycle enzymopathies. N Engl J Med, 1984, 310 (23):1500-1505.

laboratory studies often fail to distinguish between patients with NAGS deficiency and CPS deficiency, and clinicians often fail to distinguish between these two disorders and fail to perform specific genetic testing to establish the diagnosis of NAGS deficiency.

The degree of permanent neurologic impairment that develops in patients with urea cycle disorders has been shown to correlate with peak levels of ammonia[2] and the duration of hyperammonemic coma.[3] Hyperammonemia leads to multiple biochemical and structural changes in the brain, and is thought to cause swelling of astrocytes in the brain as well as pleomorphic changes in the mitochondria. Acute hyperammonemia may lead to changes in astrocyte protein expression, glutamine synthesis, nitric oxide synthesis, and changes in neurotransmitter and receptor expression. These changes may alter the brain's ability to remove additional ammonia, to regulate cerebral blood flow, to maintain energy homeostasis and neurotransmission.[4]

Prior to the availability of nitrogen scavenging and other ammonia lowering therapies, all patients with neonatal-onset urea cycle disorders died rapidly. Several studies have been published that evaluate long-term outcome in patients with urea cycle disorders. Since ammonia scavenging therapies have become available, survival has improved for neonatal-onset urea cycle disorders. One report reports that patients with neonatal-onset urea cycle defects now can survive until age 5 or longer.[5] However, there have no published outcome studies specifically evaluating long-term outcome in NAGS deficiency because the data are extremely limited due to the rarity of the disorder.

Regulatory History

This NDA is for the new molecular entity, Carbaglu (Carglumic acid), a structural analog of N-acetyl glutamate (NAG), and is intended to treat patients with N-acetyl glutamate synthase (NAGS) deficiency. The proposed indication for the product is "an adjunctive treatment for hyperammonemia due to N-acetyl glutamate synthase (NAGS) deficiency. The proposed initial dosing is 100-250 mg/kg/day given before meals in two to four divided doses daily.

Orphan designation 97-1099 was granted for this product on January 20, 1998 for the "treatment of NAGS deficiency." A Pre-IND meeting was held with the Division of Metabolic and Endocrinology Products on July 8, 2002, and the IND (IND 61,265) was received on July 17, 2003. Fast track designation was granted on May 15, 2007 for "the treatment of NAGS deficiency." A pre-NDA meeting was held on April 28, 2004. The Applicant was informed at that meeting that a chronic toxicity study in non-rodent species and a 2-year carcinogenicity study in one species would be required. On October

2 Uchino T, Endo F, Matsuda I. Neurodevelopmental outcome of long-term therapy of urea cycle disorders in Japan. J. Inher. Metab. Dis., 1998, 21:151-159

3 Msall M, Batshaw M, Suss R, et al. Neurologic outcome in children with inborn errors of urea synthesis: outcome of urea-cycle enzymopathies. N Engl J Med, 1984, 310 (23):1500-1505.

4 Enns GM. Neurologic Damage and Neurocognitive Dysfunction in Urea Cycle Disorders. Semin. Pediatr Neurol., 2008, 15:132-139

5 Summar M, Tuchman M. Proceedings of a Consensus Conference for the Management of Patients with Urea Cycle Disorders. J. Pediatr., 2001, 138: S6-S10

13, 2005, the IND was transferred from the Division of Metabolic and Endocrinology Products to the Division of Gastroenterology Products.

Carglumic acid was submitted under NDA (b) (4) and was submitted as a rolling submission. The final component of the NDA was received on July 14, 2008. However, due to significant deficiencies noted in the Agency's preliminary review of the application, the NDA was withdrawn on July 25, 2008.

Current Submission

The NDA was submitted on June 17, 2010 and was granted Priority Review status because this product would provide a significant improvement over currently available therapies for patients with NAGS deficiency. The Applicant also included data from studies under IND 68,185. This research IND was opened by M. Tuchman to study the effect of carglumic acid on several urea cycle disorders including NAGS deficiency. The Applicant obtained a letter authorizing right of reference for information contained under IND 68,185 from M. Tuchman. During the course of the review cycle, several information requests were sent to the Applicant to seeking additional information and clarification of information not included in the original submission. The Applicant submitted additional substantive clinical and clinical pharmacology information on October 14, 2009. These data were received by FDA within three months of the PDUFA goal date and were considered a major amendment to the application. Therefore, the Applicant was notified on October 15, 2009 that a three-month clock extension was required to review the additional information submitted by the Applicant, making the new PDUFA goal date March 18, 2010.

An EMDAC was convened on January 13, 2010 to discuss the data submitted in support of this Application. The reader is referred to Section 9 of this document for a summary of the details of this meeting, as well as to the Clinical Review by H. Sile. The advisory committee voted unanimously (12 to 0) that the risk/benefit analysis supported the approval of Carbaglu for the treatment of hyperammonemia due to NAGS deficiency.

The product was approved by the European Medicines Agency (EMA) in January 24, 2003 for, "Treatment of hyperammonaemia due to N-acetylglutamate synthase deficiency." The EMA labeling includes a "Special warnings and precautions for use" section that includes the following language:

> "*Therapeutic monitoring*
> Plasma levels of ammonia and amino acids should be maintained within normal limits. As very few data on the safety of carglumic acid are available, systematic surveillance of liver, renal, cardiac functions and haematological parameters is recommended.
>
> *Nutritional management*
> Protein restriction and arginine supplementation may be indicated in case of low protein tolerance."

Additionally, the EMA labeling includes the following dosage and administration instructions:

> "Carbaglu treatment should be initiated under the supervision of a physician experienced in the treatment of metabolic disorders.
>
> Based on clinical experience, the treatment may be started as early as the first day of life. The initial daily dose should be 100 mg/kg, up to 250 mg/kg if necessary. It should then be adjusted individually in order to maintain normal ammonia plasma levels (see section 4.4).
>
> In the long term, it may not be necessary to increase the dose according to body weight as long as adequate metabolic control is achieved; daily doses range from 10 mg/kg to 100 mg/kg."

Specific post-marketing requirement studies (PMRs) and final product labeling have been finalized (see section 12 [labeling] and section 13.D [PMRs] of this review for details).

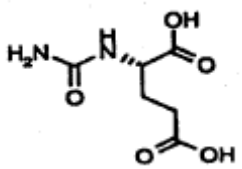
3. CMC/Device

A. General product quality considerations

The reader is referred to the chemistry review by M. Haber.

The drug substance is a derivative of a natural amino acid, L-glutamate. The chemical structure is shown in Figure 2.

Figure 2: Chemical structure of Carglumic acid



Copied from Chemistry Review, M. Haber, page 10

The drug product is a 200 mg, white, elongated, dispersible tablet, and contains 200 mg of the active ingredient, carglumic acid. The tablet is scored in three places to provide 50 mg increments per tablet. The chemistry reviewer noted that the breakability testing noted that the uniformity of content of quarter-tablets was variable, and not as good as that obtained for half-tablets.

All excipients are of compendial grade and include cellulose, microcrystalline, sodium lauryl sulfate, hydroxypropylmethylcellulose, croscarmellose sodium, silica, colloidal anhydrous, sodium stearyl fumarate, and (b) (4). The predominant excipient is (b) (4). The pharmacotoxicology review states that all the excipients to be used in the to-be-marketed formulation appear to be safe.

Two potential impurities formed from the metabolism of carglumic acid were identified as hydantoin-5-propionic acid and diaza-1,3-dion-2,4-carboxy-7-cycloheptane. However, *in vivo* studies in rats and dogs failed to detect these impurities. Additionally, (b) (4) is an impurity that arises from impurity of the starting materia (b) (4) Both the chemistry and pharmacotoxicology reviewer agree with the specifications set by the Applicant for acceptable levels of these impurities in the drug product.

The proposed expiration dating requested by the Applicant is 24 months at 5°C. The chemistry reviewer concluded that the stability data submitted in the Application supports this expiration dating.

Additionally, during labeling negotiations, the Agency requested that the Applicant provide a current National Drug Code (NDC) number, a bar code for carton and container labeling, and the name of the drug product distributor, if any. The Applicant responded late in the review cycle that a request for an NDC number was submitted on March 8, 2010, and that the request is pending. The Applicant also notified the Agency that a request for bar code exemption was also submitted to the Agency late in the review cycle. The Office of New Drug Quality Assessment (ONDQA) reviewed these issues and agreed that an approval action could still be taken if the following conditions were agreed upon with the Applicant:

3. Once the NDC numbers have been assigned by FDA, these will be added to the package insert and the carton/container labeling.
4. If the request for exemption from the requirement of using a bar code is denied by FDA, a bar code will be added to the label.

Based on an agreement by the Applicant to provide this information post-approval, the recommendation from ONDQA is for an approval action for Carbaglu.

B. Facilities review/inspection

The Division of Manufacturing and Product Quality inspected the drug product manufacturing facility operated by (b) (4) between (b) (4) At the conclusion of the inspection, an FDA Form 483 was issued to the manufacturing facility citing two major inspectional observations uncovered during the inspection, as follows:

1. The written stability program for drug products does not include reliable test methods. Specifically, the methodology used to test for impurities in the finished product are not robust. Additionally, determination of impurities by HPLC method showed out of specification results for hydantoin-5-Propionic Acid (HPA).

2. Routine calibration of mechanical and electronic equipment is not performed according to a written program designed to assure proper performance. Specifically, calibration of the of (b) (4) step was not performed consistently. Additionally, calibration of the (b) (4) step was not performed.

The manufacturer, (b) (4) provided a response to these deficiencies to the Office of Compliance on November 19, 2009. However, these responses were deemed to be insufficient, and the Office of Compliance sent a letter on February 1, 2010, requesting additional information to resolve these deficiencies. The Office of Compliance received a response from (b) (4) on March 10, 2010. The Office of Compliance reviewed these responses and found them to be satisfactory. Therefore, an "Acceptable" rating was issued for the manufacturing facility and a recommendation for an Approval action for Carbaglu on March 15, 2010 by the Office of Compliance.

Final Recommendation
The chemistry reviewer recommended that a Complete Response action for the Application due to unresolved manufacturing deficiencies at the drug product manufacturing facility, (b) (4). However, the tertiary reviewer for the Office of New Drug Quality Assessment (ONDQA), E. Morefield, concurred with the final recommendation from ONDQA for approval of Carbaglu because the manufacturing site had recently received an acceptable recommendation (March 15, 2010), and the labeling had been acceptably revised. However, the Applicant has agreed to provide the following information post-approval:

1. NDC numbers, once assigned by FDA, will be added to the package insert and the carton/container labeling.
2. If the request for exemption from the requirement of using a bar code is denied by FDA, a bar code will be added to the label.

4. Nonclinical Pharmacology/Toxicology

The reader is referred to the Pharmacology/Toxicology Review by Y.C. Ng and to the Supervisory Pharmacologist memo by D. Joseph.

Acute and chronic toxicity studies were conducted in rats. Single oral doses of up to 2800 mg/kg, and intravenous doses of up to 238mg/kg were tolerated in rats. Chronic oral toxicity studies (2-week and 26-week) were conducted. The highest doses of carglumic acid tested in the 2-week study (2000mg/kg) produced death in most rats within 2-3 days of treatment and these deaths were considered drug-related. Deaths were also noted at lowest dose tested (250mg/kg), but these deaths were attributed to gavage errors. The highest dose of carglumic acid tested in the 26-week study (1000mg/kg) produced necrotizing inflammation of the Harderian gland and multicellular hepatic necrosis. Interstitial mononuclear cell aggregation in the kidney was observed at both 500 mg/kg and 1000 mg/kg dosing.

Genotoxicity studies as evaluated using the Ames mutagenicity test, in vitro chromosomes aberration assay in human peripheral blood lymphocytes, and the in vitro macronucleus assay in rates were all negative. Reproductive toxicology studies in rats given oral doses of carglumic acid up to 2000gm/kg/day failed to detect drug-related fetal malformation.

The reviewer also noted that during a pre-IND meeting held on September 24, 2002, the Agency requested that an additional chronic toxicity study in a nonrodent species be conducted to support the NDA. The Applicant disputed the requirement for an additional chronic toxicity study citing "lack of toxicity observed in a relevant species," as well as a lack of adverse events reported with chronic dosing in NAGS deficiency patients. However, the reviewer clinical experience in humans does not preclude obtaining nonclinical toxicity studies because detailed information relating to target tissue injury (e.g., histopathology) cannot otherwise be obtained. The Agency reiterated this position to the Applicant in a correspondence on September 26, 2008. Additionally, the reviewer noted that the Applicant has not performed nonclinical carcinogenicity studies. However, the Applicant has agreed to conduct a two-year carcinogenicity study in a single species as post-marketing requirement.

Final Recommendation

The pharmacotoxicology reviewer recommends an Approval action for Carbaglu. Additionally, as described above, the pharmacotoxicology reviewer recommends that the Applicant perform two additional post-marketing requirement studies to further evaluate the safety of Carbaglu. The first study should be conducted as a chronic (9-month) toxicity study in a nonrodent species, and the second study should be a two-year carcinogenicity study in a single species.

During negotiations with the Applicant regarding post-marketing requirement studies, there was disagreement regarding the requirement to perform a chronic toxicity study in a nonrodent species. The primary and secondary pharmacotoxicology reviewers recommended that this study be performed. However, the Applicant argued that chronic (up to 21 years) human exposure to carglumic acid precluded the requirement to perform additional toxicology studies in animals. This issue was reviewed by A. Jacobs, Associate Director for Pharmacology/Toxicology, CDER. Her review, dated March 15, 2010, states concurrence with the primary reviewer regarding an approval action for Carbaglu. However, she did not concur with the requirement for a chronic study in an additional nonrodent species, or for the requirement to perform a carcinogenicity study in a single animal species. The reasons provided to support this recommendation included that the drug is life-saving, the number of affected individuals is relatively small, and the animals that will be tested will not have hyperammonemia so that adverse events observed in these animals may not be relevant to patients.

5. Clinical Pharmacology/Biopharmaceutics

The reader is referred to the Clinical Pharmacology review by K. Estes.

The Applicant provided two Phase 1 studies, a bioequivalence study and a mass balance study in support of the clinical pharmacology section of the NDA. The Applicant did not perform standard Phase 3 clinical pharmacology studies. However, there were limited clinical pharmacology data available for review from the retrospective case series of 23 patients treated with Carbaglu.

The pharmacokinetic profile of Carbaglu was determined based on a bioequivalence (BE) study in 12 healthy male volunteers. This study was performed to bridge the to-be-marketed tablet formulation with the previous pharmaceutical grade formulation. The results of the study provide some information regarding the PK profile in healthy volunteers (i.e., Tmax, apparent volume of distribution, and terminal half-life). Additional data on the pharmacokinetic profile in patients with NAGS deficiency were limited to six patients for whom sufficient dosing information was available. However, a direct comparison between the PK profile in healthy volunteers and patients with NAGS deficiency could not be performed due to the limited data available in NAGS deficiency patients. Therefore, PK data that were used for product labeling are based on the PK data in healthy volunteers.

The pharmacodynamic effect of Carbaglu was evaluated using reduction of plasma ammonia levels in the 23 patients reviewed in the retrospective case series. There were no formal pharmacodynamic studies performed, and no dose response relationship could be established based on the data available for review. Additionally, *in vitro* studies of the effect of Carbaglu on the cytochrome P450 enzyme system did not address the potential for Carbaglu to inhibit or induce cytochrome P450, and formal drug-drug interactions have been performed. Therefore, the reviewer could not specifically conclude whether or not Carbaglu has the potential to produce drug-drug interactions.

The effect of Carbaglu on QT interval was assessed in isolated canine Purkinje fibers and in conscious dogs. There was no statistically significant effect on action potential parameters or QT interval in doses up to 1000mg/kg. Additionally, review of the clinical data in NAGS deficiency patients treated with Carbaglu for up to 16 years, there have been no reports of QT interval prolongation; however, a thorough QT study has not been performed in humans. The reviewer is not recommending an additional thorough QT study in humans be performed due the lack of evidence of cardiac effects in nonclinical studies and lack of evidence of effect on QT interval in long-term use of Carbaglu in NAGS deficiency patients.

The effect of specific intrinsic factors that may affect elimination (i.e., age, gender, hepatic insufficiency, and renal impairment) were not studied and are not known. However, the reviewer concluded that intrinsic factors are not likely to be useful in defining exposure or response to Carbaglu because of the extremely small number of patients with NAGS deficiency.

Final Recommendations
The clinical pharmacology reviewer recommends an Approval action for Carbaglu. Additionally, the reviewer recommended changes to "Section 12: Clinical Pharmacology" of the labeling for Carbaglu based on the clinical pharmacology data reviewed (see final product labeling for details). Finally, due to the limited information available regarding the metabolism of carglumic acid, the clinical pharmacology reviewer recommended one post-marketing requirement (PMR) study be performed by the Applicant to evaluate the potential for drug interactions. The study should evaluate the effect of carglumic acid on the cytochrome P450 enzyme system *in vitro*.

6. Clinical Microbiology

Clinical Microbiology considerations do not apply to this application because Carbaglu is not an antimicrobial agent.

7. Clinical/Statistical- Efficacy

The reader is referred to the Clinical review by H. Sile and V. Elgin. A formal statistical review was not performed because the retrospective, unblinded, and uncontrolled nature of the data precluded any meaningful formal statistical analyses of the data. Under these conditions, any statistical inference from confidence intervals and/or p-values is uninterpretable, and consequently, was not utilized to inform clinical decision making.

As stated above, support for the clinical efficacy of Carbaglu relies on data from a retrospective case series in 23 patients who received treatment with carglumic acid over a 16-year period. Additionally, the Applicant provided data from an ongoing study under IND 68,185. The objective of the study under IND 68,185 was to evaluate the effect of carglumic acid on ureagenesis in stable patients with urea cycle disorders (including NAGS deficiency). Interim data from this study includes 3 NAGS deficiency patients who were treated for 3 days with Carbaglu. The data from this study were extremely limited and do not provide substantive support for the effect of Carbaglu in the treatment of hyperammonemia due to NAGS deficiency. Therefore, this memo will focus on the data from the retrospective case series.

Retrospective case series
The purpose of this retrospective case series was to provide information on the effect of Carbaglu in the treatment of patients with hyperammonemia due to NAGS deficiency. The Applicant did not perform any prospective clinical trials evaluating the effect of Carbaglu in NAGS deficiency patients. The efficacy and safety data provided from the retrospective case series was obtained from review of individual patient medical records collected over from 1987 through 2008. All patients received at least one dose of carglumic acid, and patients were treated at 14 sites outside of the United States.

The Applicant chose to evaluate the efficacy of Carbaglu based on three clinical laboratory tests; plasma ammonia, plasma glutamine, and plasma citrulline. Elevated plasma ammonia levels are a hallmark of patients with urea cycle disorders including NAGS deficiency. Severe elevations in plasma ammonia level are associated with severe neurologic sequelae and death. Therefore, plasma ammonia level would be considered a clinically relevant efficacy endpoint in NAGS deficiency. Plasma glutamine levels are also elevated in NAGS deficiency and appear to play a role in the pathogenesis of CNS complications in urea cycle disorders[6], however, plasma glutamine level cannot be considered a clearly clinically relevant endpoint because decreases in plasma glutamine level have not yet been associated with clinical improvement separate from improvements in plasma ammonia levels. Finally, plasma citrulline levels are low in patients with NAGS deficiency and would be expected in increase with treatment. However, plasma citrulline levels have not yet been associated with clinical improvement in patients with urea cycle disorders including NAGS deficiency.

Additionally, the Applicant collected neurologic outcomes data in all patients where data were available. As stated above, neurologic outcome in patients with urea cycle disorders who develop hyperammonemic coma is poor. Additionally, based on natural history data, severe neurocognitive impairment and mortality are high in patients with urea cycle disorders who are left untreated.

Of the 23 patients included in the retrospective case series, only 13 patients had complete data available for plasma ammonia levels (see Figure 3). Three patients were excluded from the efficacy analysis because they were asymptomatic and found to heterozygotes for NAGS deficiency. These three patients would not likely develop either hyperammonemia or clinical symptoms and, therefore, treatment with Carbaglu was not indicated. However, data from these patients were included in the safety analysis. An additional three patients had normal baseline ammonia levels, and therefore normalization of plasma ammonia levels could not be evaluated, and four patients had incomplete documentation of plasma ammonia levels.

6 Enns GM, Neurologic Damage and Neurocognitive Dysfunction in Urea Cycle Disorders, Semin. Pediatr. Neurol., 2008, 15:132-139

Figure 3: Review of evaluable patients from retrospective case series

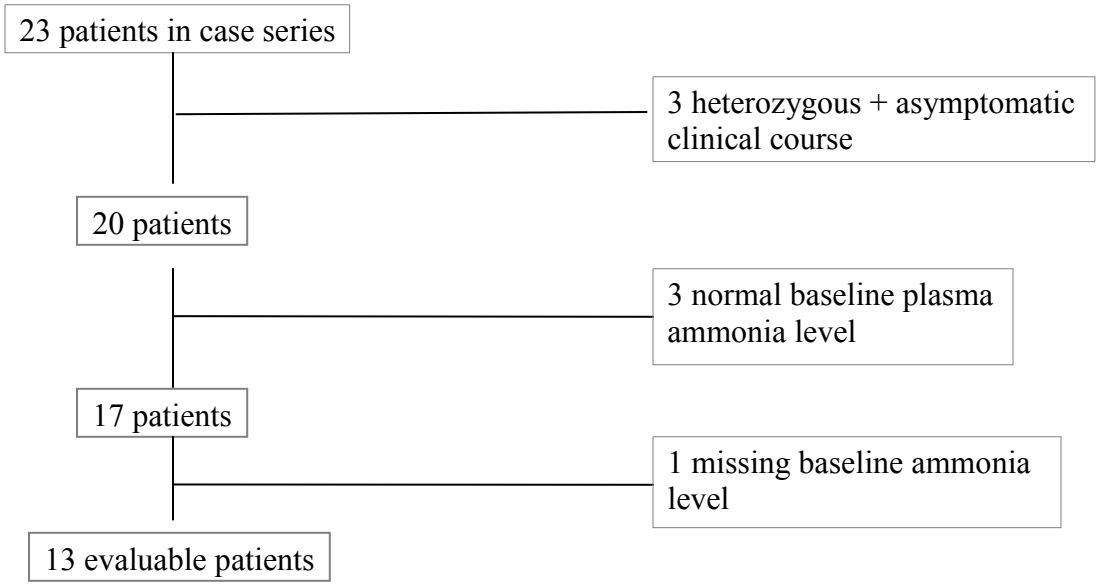


Figure modified from advisory committee presentation by H. Sile

Effect on Plasma Ammonia

The Applicant evaluated the effect of carglumic acid treatment on both "short-term" and "long-term" ammonia level. The Applicant defined short-term treatment effect as the effect on plasma ammonia level within 7 days of first carglumic acid treatment. The long-term response was evaluated by examining the last available plasma ammonia level while on treatment with carglumic acid. The average length of treatment in these patients was long; median treatment length was 5.8 years with a range of 1.3 to 16 years. Normal ammonia level ranges between 60-100 μmol/L in neonates and is ≤ 50 μmol/L for infants, children, and adults. All 13 patients had elevated plasma ammonia levels at baseline with a mean baseline plasma ammonia level of 270 μmol/L. By Day 1, plasma mean plasma ammonia level decreased to a mean of 181 μmol/L, and by Day 3, all patients with data (N=5) had normal plasma ammonia levels (see Table 1). Additionally, long-term treatment with Carbaglu was associated with sustained normalization of plasma ammonia levels. Mean plasma ammonia level was 23 μmol/L, and all patients had plasma ammonia in the normal range (9-34 μmol/L) (see Table 1). Additionally, the Applicant informed the advisory committee that all concomitant ammonia lower therapies were removed from patients at the time of the long-term plasma ammonia level measurement. Therefore, Carbaglu was the only treatment that the patients were receiving in the long-term follow up. These data are limited in both quality and quantity, but normalization of plasma ammonia levels would not be expected long-term in untreated patients with NAGS deficiency. Therefore, when compared to natural history data, the effect of Carbaglu appears to be clinically significant.

Table 1: Change in plasma ammonia level (µmol/L)

	Baseline	Day 1	Day 2	Day 3	Long-term	Change from Baseline
N	13	10	8	5	13	13
Ammonia (µmol/L)						
Mean (±SD)	270 (358)	181 (357)	69 (78)	27 (11)	23 (7)	-248 (363)
Median	157	65	44	25	24	-131
Range	72-1428	25-1190	11-255	12-42	9-34	-1419 to -47

Table modified from advisory committee presentation by H. Sile

Effect on Plasma Glutamine

The Applicant also included supportive data on the effect of carglumic acid on plasma glutamine levels. Normal plasma glutamate levels vary with age; normal adult values range from 410 to 860 µmol/L.[7] Plasma glutamine levels appear to decrease on days 1 and 2 and long-term in NAGS deficient patients for whom data were available (see Table 2). However, only three patients had plasma glutamine levels on Day 2. Thus, short-term data for plasma glutamine are extremely limited. Long-term response was based on the last available glutamine value while on treatment with Carbaglu. Again, the average length of treatment in these patients was long; median treatment length was 5.8 years with a range of 1.3 to 16 years. These findings suggest that plasma glutamine levels improve with short and long-term treatment with Carbaglu. However, clear conclusions about the effectiveness of carglumic acid on plasma glutamine levels cannot be made because of the severely limited quantity and quality of the data.

Table 2: Change in plasma glutamine level (µmol/L)

	Baseline	Day 1	Day 2	Long-term	Change from Baseline
N	16	6	3	18	15
Ammonia (µmol/L)					
Mean (±SD)	957 (453)	545 (102)	479 (164)	561 (195)	-497 (404)
Median	998	527	503	516	-570
Range	131-1961	426-670	305-631	353-1193	-1532 to -203

Modified from clinical review, table 63 and 68, pages 149 and 158, by H. Sile and V. Elgin

Effect on Neurocognitive Outcome

The Applicant also retrospectively reviewed the medical records of 23 NAGS deficiency patients treated with Carbaglu for available neurocognitive outcome information. Only 17/23 patients had neurological outcome data available. Of these 17 patients 3 were described as having a "normal" baseline neurological or neurocognitive status, while 14 patients were described as having an "abnormal" baseline neurological or neurocognitive status. As stated earlier, neurological and neurocognitive assessments were not performed with a standard methodology, with validated tools, or using consistent terminology. Therefore, the data cannot be used to make generalizations about the effect of treatment with Carbaglu on neurocognitive or neurologic outcome in patients with

7 Tuchman M, Yudkoff M. Blood Levels of Ammonia and Nitrogen Scavenging Amino Acids in Patients with Inherited Hyperammonemia. Mol Genet and Metabol., 1999, 66:10-15

NAGS deficiency. Nevertheless, all 3 patients with normal neurological status at baseline remained normal throughout treatment with Carbaglu, and 9/14 patients with abnormal baseline neurologic status had sustained "improvement" in their neurological status. It should be noted that these improvements would not be expected without effective treatment based on the natural history of neurocognitive outcome in patients with urea cycle disorders. Therefore, it appears that treatment with Carbaglu may lead to improved long-term neurologic and neurocognitive outcomes. Prospective collection of long-term neurologic and neurocognitive outcomes is needed to better evaluate the effect of Carbaglu on these outcomes.

Figure 4: Neurologic outcome in patients from retrospective case series with evaluable data

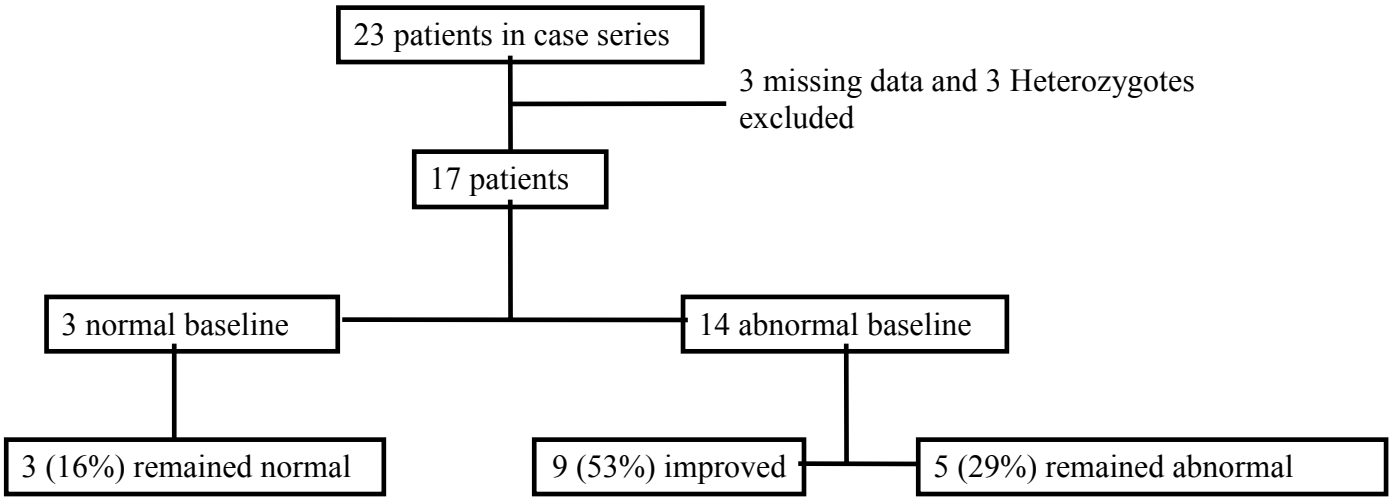


Table modified from advisory committee presentation by H. Sile

The data presented on the effect of Carbaglu on plasma ammonia levels were based on 13 evaluable patients. However, of these 13 patients, only 5 patients did not receive any concomitant ammonia lowering therapies (i.e., hemodialysis, sodium phenylacetate or sodium phenylbutyrate) during an episode of acute hyperammonemia. Therefore, the effect of Carbaglu independent of the effect of other ammonia lowering therapies in the treatment of acute hyperammonemic episodes in patients with NAGS deficiency cannot be evaluated. However, all patients were receiving Carbaglu as sole therapy at the long-term follow up measurement. Therefore, it appears that Carbaglu may be appropriate as single therapy for the maintenance of normal plasma ammonia levels in patients with NAGS deficiency. Additionally, the data regarding dose adjustments after patients achieved normal plasma ammonia levels are also extremely limited. It appears that most patients required 20-50% less Carbaglu with long-term treatment.

Final Recommendation

Although the data submitted in support of the efficacy of Carbaglu in the treatment of hyperammonemia due to NAGS deficiency were limited and retrospectively obtained, the data appear to represent a substantial number of patients with NAGS deficiency given the

extreme rarity of the condition (estimated 25-50 patients known worldwide). Additionally, the data support the short and long-term effectiveness of Carbaglu in treatment of hyperammonemia based on the rapid and sustained normalization of plasma ammonia levels in all NAGS deficiency patients for whom data were available. However, I agree with the clinical reviewer's recommendation that Carbaglu be used as an *adjunctive* treatment for hyperammonemia in patients with NAGS deficiency due to the severely limited data in patients who did not receive any other concomitant ammonia lower therapies. This recommendation was also made by the advisory committee (see Section 9). Furthermore, clear recommendations regarding maintenance dosing of Carbaglu must be determined based on careful monitoring of plasma ammonia levels because insufficient data were available to determine a standard, maintenance dose or dosing regimen.

8. Safety

The reader is referred to the Clinical review by H. Sile and V. Elgin.

The safety database consisted of safety information on 23 NAGS deficiency patients in a retrospective case series treated with at least one dose of Carbaglu. There were an additional seven patients who received Carbaglu for three days under IND 68,185. However, the patients treated under IND 68,185 received a short exposure to Carbaglu compared to the patients in the retrospective case series. Therefore, this review will focus on the data collected as part of the retrospective case series only. Identification of drug-related adverse events is challenging as patients with NAGS deficiency would be expected to develop significant morbidity related to episodes of hyperammonemia. Furthermore, the retrospective review of the clinical data in these 23 patients was not designed to systematically or prospectively collect adverse event data. The reporting of adverse events was based on the review of medical records from treating physicians. Therefore, complete safety data on Carbaglu are lacking. Nevertheless, the safety database includes adverse event information NAGS deficiency patients who have received treatment with Carbaglu for up to 21 years, with 14/23 patients having received treatment with Carbaglu for at least 5 years. Additionally, there are seven patients treated with Carbaglu for 3 days under IND 68,185. These data are extremely limited due to the short duration of exposure and safety data collected from this study were not revealing and will not be discussed further in this memo.

There were two deaths reported in the retrospective case series. Patient 33 was an 11 year-old girl who was diagnosed with NAGS deficiency in infancy. She was treated with Carbaglu since 1996. In 2007, she developed severe hyperammonemia associated with pneumonia. She was hospitalized by later died. Her death was assessed as unrelated to treatment with Carbaglu based on her treating physicians report. The second patient death occurred in a 9 year-old girl who was diagnosed with NAGS deficiency prior to birth due to a sibling who had previously died from NAGS deficiency. Treatment with chemical grade carglumic acid was initiated on day of life 1. However, the medical record notes that there was some problem with episodic hyperammonemia throughout the child's life presumed to be due to noncompliance with treatment and diet. The patient

was hospitalized in 2003 to be "weaned off" of Carbaglu, but she developed fever, pneumonia, and died prior to discharge from the hospital. The treating physician assessed that the patient's death was unrelated to treatment with Carbaglu. The clinical reviewer agrees with both the treating physicians' assessments.

There were 30 non-fatal serious adverse events (SAEs) reported in 10 patients in the retrospective case series. Vomiting was the most common SAE reported (in 6 patients). Other SAEs include headache, seizures, pneumonia, dehydration, fecal and urinary incontinence, somnolence, and paraplegia. None of the SAEs were assessed as related to treatment with Carbaglu and many of these events may be related to the patient's underlying disease.

Overall, adverse events were reported in all 23 patients. Adverse events that were observed in at least three patients in the retrospective case series included vomiting, abdominal pain, infections, headache, fever, and anemia (see Table 3). Additionally, two patients were noted to have dysgeusia which their treating physician assessed as related to Carbaglu treatment.

Table 3: Adverse events occurring in 3 or more patients in the retrospective case series

System Organ Class	Subjects N (%)
Total	**23 (100)**
Gastrointestinal disorders	**10 (43.5)**
vomiting	6 (26.1)
abdominal pain	4 (17.4)
diarrhea	3 (13.0)
Infections and Infestations	**10 (43.5)**
tonsillitis	4 (17.4)
infection	3 (13.0)
nasopharyngitis	3 (13.0)
General disorders and administration site conditions	**7 (30.4)**
Pyrexia	3 (13.0)
Nervous System disorders	**6 (26.1)**
headache	3 (13.0)
Ear and labyrinth disorders	**4 (17.4)**
ear infection	3 (13.0)
Blood and lymphatic system disorders	**5 (21.7)**
anemia	3 (13.0)

From clinical review, table 72, page 168, H. Sile and V. Elgin

Significant laboratory findings include the development of anemia in 3 patients while treated with Carbaglu. There is no follow-up information provided for these patients, but none of these events of anemia were considered serious. Additionally, there was only one patient in the retrospective case series that developed elevation in transaminase (AST), but ALT, total bilirubin, and the patient's coagulation profile remained normal. A follow-up AST level was normalizing, but no additional follow-up information documenting normalization of AST was provided. It should be noted that the labeling for Carbaglu approved by EMA includes a report of uncommonly occurring (≥ 1/1,000 to < 1/100) adverse reaction of increased transaminases. The clinical reviewers found no increased incidence of transaminase elevation in the safety data reviewed. No other adverse events relating to vital signs, ECG, or other laboratory studies were uncovered. Again, the lack of systematic and prospective plan for collection of adverse events may have lead to incomplete information on the true incidence these adverse events. No special safety studies or Immunogenicity studies were performed.

Additionally, high doses of Carbaglu (650-750 mg/kg/day) were associated with symptoms consistent with glutamate intoxication; tachycardia, sweating, bronchial hypersecretion, elevated body temperature, and restlessness.[8]

Final Recommendation
The safety database for Carbaglu includes 23 NAGS deficiency patients treated with Carbaglu for up to 21 years. The majority of patients 14/23 were treated with Carbaglu for at least 5 years. There were 2 patient deaths that were assessed as not related to treatment with Carbaglu and 10 patients who developed serious adverse events that were assessed as not related to treatment. Many of the serious adverse events reported appear to be related to the patient's underlying disease. Thus, I agree with the clinical reviewers that the safety profile of Carbaglu appears reasonable based on the small number of deaths, serious adverse events, and significant adverse events reported. Nevertheless, the retrospective nature of the safety data collected, and the lack of systematic and prospective plan for reporting of adverse events precludes the ability to make clear conclusions regarding the long-term safety of Carbaglu.

9. Advisory Committee Meeting

The reader is referred to the Advisory Committee transcript located at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM200613.pdf for full details of the meeting.

An Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) was convened on January 13, 2010 to discuss the data submitted in support of the efficacy and safety of Carbaglu in the treatment of hyperammonemia due to NAGS deficiency. The questions

8 Schubiger G, Bachmann C, Barben P, et al, N-acetylglutamate synthetase deficiency: diagnosis, management and follow-up of a rare disorder of ammonia detoxification. Eur. J. Pediatr., 1991, 150:353-356.

that the committee was asked to answer were largely based on whether the quantity and quality of evidence submitted provided substantial evidence of the efficacy of Carbaglu in the treatment of NAGS deficiency and whether the risk/benefit profile of Carbaglu supported the approval of Carbaglu for the treatment of NAGS deficiency.

The committee voted unanimously (12 yes, 0 no, 0 abstain) that the clinical data submitted for the effectiveness of Carbaglu in the treatment of hyperammonemia in NAGS deficiency met legal standard for substantial evidence. In support of this vote, committee members noted that the pathophysiology of disease and the mechanism of action of the drug were both well understood. Additionally, the committee members noted that changes in plasma ammonia levels provided an objective, and clinically relevant measure of efficacy, and that the changes in plasma ammonia level were demonstrated to be both robust and sustained.

Other recommendations made by the advisory committee include the following:

1. Dose adjustments for maintenance dosing should be based on individual patient plasma ammonia level but will likely be modified to 20-50% of the patient's acute dose.
2. Other adjunctive ammonia lowering therapies should be used during episodes of acute hyperammonemia.
3. Careful monitoring of plasma ammonia level should be required for patients receiving treatment.
4. Additional nonclinical studies evaluating chronic toxicity and carcinogenicity should be performed
5. A registry should be established for NAGS deficiency patients receiving treatment with Carbaglu to evaluate long-term safety.

10. Pediatrics

Carbaglu is an orphan product so the Pediatric Research Equity Act does not apply. There was no formal pediatric consult. The data provided in the application was adequate to support the safety and effectiveness of Carbaglu as an adjunctive treatment for hyperammonemia for all pediatric NAGS deficiency patients.

11. Other Relevant Regulatory Issues

The Division of Scientific Investigations (DSI) completed a review dated December 4, 2009, and the review notes that there were no concerning issues identified. The Applicant provided adequate documentation of financial disclosures. None of the investigators involved in studies submitted in the NDA received compensation from the Applicant, proprietary interest in this product or significant equity in the Applicant's company. Additionally, DSI audited the SGS Aster SAS, the clinical site performing the analytical and clinical portion of a bioequivalence study submitted in the application. A Form 483 was issued to SGS Aster SAS on January 8, 2010, the based on findings noted during the inspection. These deficiencies include:

1. Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation and informed consent.
2. An adequate final report was not provided to the sponsor shortly after completion of the investigator's participation in the investigation.
3. An investigation was not conducted in accordance with the investigational plan.

However, despite these deficiencies, and the issuance of a Form 483, a memorandum from DSI reviewer, A. Dasgupta, dated March 5, 2010 stated that these deficiencies did not compromise subject safety and should not impact study outcomes. Therefore, the original recommendations from DSI that data generated from sites inspected are reliable and can be used in support of the NDA are not changed. The memorandum also recommends that the firm should take corrective action to prevent the deficiencies from repeating in future studies.

Manufacturing facility inspections were completed on (b) (4). Deficiencies cited during this inspection were related to the manufacturer (b) (4) in a Form 483 correspondence submitted at the end of the inspection. The manufacturer responded to these deficiencies on November 19, 2009. However, these responses were not completely satisfactory and an information request was sent to (b) (4) by the Office of Compliance on February 1, 2010. A response to this information request was received late in the review cycle. The Office of Compliance reviewed the manufacturer's responses to the information request and deemed the responses as adequate. Therefore, the Office of Compliance issued an "acceptable" rating for the manufacturing facility and recommended an approval action for Carbaglu on March 15, 2010.

12. Labeling

A. Proprietary Name

The Applicant proposed the trade name of "Carbaglu" for their product under NDA 22-562. A review of the trade name was performed by Z. Oleszczuk in the Division of Medication Errors Prevention and Analysis (DMEPA). The trade name "Carbaglu was found to be acceptable by DMEPA.

B. Physician Labeling/Carton and Container Labeling

Final labeling for Carbaglu was satisfactorily negotiated during the current review cycle. The final labeling conforms to the Physician Labeling Rule (PLR) format. The reader is referred to final labeling for Carbaglu for complete details. Highlights of labeling negotiated to date for Carbaglu are presented below.

(b) (4)

2 Page(s) of Draft Labeling has been Withheld in Full immediately following this page as B4 (CCI/TS)

(b) (4)

13. Recommendations/Risk Benefit Assessment

A. Recommended Regulatory Action

In the opinion of this reviewer, the data in this application support the approval of Carbaglu for the adjunctive treatment of hyperammonemia due to NAGS deficiency. The data in this application also provide sufficient information to construct product labeling that is necessary for the safe and effective use of the product in patients with NAGS deficiency. As stated above, the primary and secondary pharmacotoxicology reviewer both recommended that a chronic (9-month) toxicology study in a nonrodent species be conducted as a post-marketing requirement. However, the tertiary pharmacotoxicology reviewer did not concur with the recommendation. I am in agreement with the recommendations for one additional post-marketing requirement study, a carcinogenicity study in a single species, based on the reviews of all three of the pharmacotoxicology reviewers. I am also in agreement with the advisory committee recommendation that a patient registry be implemented to evaluate the long-term safety of Carbaglu. The primary clinical reviewer did not make a specific recommendation regarding the requirement to perform additional clinical post-marketing studies. Finally, I am in agreement with the recommendation from the primary clinical pharmacology reviewer regarding the need for post-marketing studies to evaluate the potential for drug-drug interactions with Carbaglu. However, after further discussion with clinical pharmacology and the Applicant, I recommend that these studies be conducted as post-marketing commitment studies rather than post-marketing requirement studies as outlined below.

Finally, outstanding issues relating to manufacturing deficiencies at the drug product manufacturing facility were satisfactorily resolved late in the review cycle. The Office of Compliance reviewed responses by the manufacturer submitted on March 10, 2010, and deemed these responses adequate. However, the Office of Compliance also recommends that follow up of the deficiencies adequately addressed by the manufacturer be reviewed during a Post-Approval Inspection that will be scheduled by the Office of Compliance. Therefore, the Office of Compliance issued an "acceptable" rating for the Carbaglu manufacturing facility and a recommendation for an Approval action for Carbaglu on March 15, 2010. I agree with this determination.

B. Risk Benefit Assessment

I am in agreement with the overall recommendation for an Approval action from the nonclinical, clinical pharmacology and clinical reviewers. The data presented in the application support the overall safety and effectiveness of Carbaglu as an adjunctive treatment for hyperammonemia in NAGS deficiency patients. However, the long-term safety of the product cannot be established without the implementation of recommended nonclinical and clinical postmarketing requirement studies (see Section 13.D). These studies have been fully negotiated with the Applicant.

C. Recommendation for Postmarketing Risk Evaluation and Management Strategies

This reviewer agrees with all other review disciplines that postmarketing risk evaluation and management strategies (REMS) are not recommended for Carbaglu.

D. Recommendation for other Postmarketing Requirements and Commitments

Several outstanding safety issues remain unresolved and include nonclinical, clinical pharmacology and clinical safety issues. The rationale for these additional studies has been previously discussed above. Therefore, the following safety studies are recommended as post-marketing requirement (PMR) studies have been successfully negotiated with the Applicant:

Nonclinical

1. A 2-year carcinogenicity study in a single rodent species

Clinical

1. A registry of patients with NAGS deficiency being treated with carglumic acid to obtain long-term clinical safety information. Data to be collected will include patient demographics, details of treatment with carglumic acid, other therapies for hyperammonemia and dietary protein management, clinical status, neurocognitive and psychomotor outcomes, growth and development stages, and adverse events. Information from this registry should be submitted annually (in annual reports) with a final report submission at 15 years post-approval.

2. A study of the effects of carglumic acid on pregnancy and fetal outcomes. This study can be performed as a sub-study within the registry described above. Information on pregnancy and fetal outcomes should be submitted annually (in annual reports) and included in the final report submission on the registry at 15 years post-approval.

There were two additional post-marketing commitment studies negotiated with the Applicant. Both of these post-marketing commitment (PMC) studies will evaluate the potential for drug-drug interactions with Carbaglu.

Clinical Pharmacology Post-marketing Commitment Studies

1. We acknowledge your plans to complete and submit the final study report for the on-going study entitled, "*In vitro* metabolic stability of N-carbamyl [14C]-glutamic acid in rat, mini-pig, dog, monkey and human hepatocytes." The viability of the hepatocytes in terms of various cytochrome P450 enzyme activities should be documented in the report.

2. An *in vitro* study to assess the potential for carglumic acid to inhibit or induce the Cytochrome P450 enzymes.

E. Recommended Comments to Applicant

Based on the recommended Approval action for Carbaglu, the recommended comments to the Applicant relate to additional post-marketing requirement (PMR) and commitment (PMC) studies. Specific PMR and PMC studies are discussed above in section 13.D. Additionally, the Applicant should be informed of the need for an established NDC number, bar code (if an exemption is denied by FDA), and drug product distributor (if any) to complete carton, contain, and label requirements. These items are currently pending, but the Office of New Drug Quality and Assessment have agreed that the Applicant may submit this information post-approval. The Approval letter should state that the Applicant has agreed to the following:

1. Once the NDC numbers have been assigned by FDA, these will be added to the package insert and the carton/container labeling.
2. If the request for exemption from the requirement of using a bar code is denied by FDA, a bar code will be added to the label.

The reader is directed to the Approval Letter for specific details.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22562	ORIG-1	ORPHAN EUROPE	CARBAGLU (CARGLUMIC ACID)

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

/s/

LYNNE P YAO
03/16/2010
CDTL memo