CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-562

OFFICE DIRECTOR MEMO

MEMORANDUM

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

DATE: March 18, 2010

FROM: Julie Beitz, MD

SUBJECT: Office Director Memo

TO: NDA 022562 Carbaglu (carglumic acid) Tablets
Orphan Europe SARL

Summary

Carbaglu (carglumic acid) Tablets have been evaluated for the treatment of NAGS deficiency, the rarest of the urea cycle enzyme deficiencies. Carbaglu is a structural analog of N-acetylglutamate (NAG), an essential cofactor for the enzyme carbamyl phosphate synthetase (CPS) which catalyzes the first step of the urea cycle (formation of carbamyl phosphate from ammonia, bicarbonate and two molecules of ATP). NAG is made in the mitochondrial matrix when acetyl CoA and glutamate combine in a reaction catalyzed by NAG synthetase (NAGS).

Children born with complete urea cycle enzyme deficiencies appear normal during the first hours of life, but rapidly develop symptoms of hyperammonemia. Prior to the introduction of alternative waste nitrogen excretion pathway therapies, survival with dietary nitrogen management alone was low. Among 28 patients with complete urea cycle enzyme deficiencies, the one-year survival rate was 14% and three of the four survivors had mental retardation.[1] With the use of sodium phenylacetate and sodium benzoate, and supplementation with arginine or citrulline, the one-year survival rate among 26 patients was reported by Msall et al. to be 92%. Twenty of 24 or 83% of children survived beyond one year. Most survivors, however, had at least one developmental abnormality, and 46% had multiple deficits (including mental retardation, cerebral palsy, and seizures) when evaluated at ages ranging from 12 to 74 months. These authors concluded that prolonged neonatal hyperammonemic coma is associated with neurocognitive impairment.[2] Prospective neonatal therapy, after prenatal diagnosis by DNA or biochemical analysis, is thought to prevent neonatal hyperammonemia and lead to more favorable neurologic outcomes.

Late onset NAGS deficiency, in which the degree of residual enzyme activity is heterogeneous, has a variable age of onset. Survival of these patients approaches 100%. Despite a relatively low number of hyperammonemic episodes, however, roughly half of affected individuals develop moderate to severe neurologic impairment.[3] Psychiatric symptoms, including hyperactive behavior, mood disturbances, self-injurious behavior, and psychosis, may also occur.[4]

This memo documents my concurrence with the Division of Gastroenterology Product's (DGP's) recommendation to approve Carbaglu (carglumic acid) Tablets for pediatric and adult patients as adjunctive treatment of acute hyperammonemia due to NAGS deficiency, and as maintenance treatment of chronic hyperammonemia due to NAGS deficiency. The deficiencies identified during a November 2009

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[1] Shih, V.E. (1976) Hereditary urea cycle disorders. *In:* Grisolia, S., Baguena, R. Mayor R., *eds.,* The urea cycle. New York: John Wiley, 367-414.
[2] Msall, M., Batshaw, M. L., Suss, R., et al. (1984) Neurologic outcome in children with inborn errors of urea synthesis: outcome of urea-cycle enzymopathies. *N. Engl. J. Med., 310:* 1500- 1505.
[3] Nassogne, M.C., Heron, B., Touati, G., et al. (2005) Urea cycle defects: management and outcome. *J. Inherit. Metab. Dis. 28:* 407-414.
[4] Gropman, A.L., Summar, M., and Leonard, J.V. (2007) Neurological implications of urea cycle disorders. *J. Inherit. Metab. Dis. 30:* 865-879.

inspection of the finished dosage manufacturing facility have been adequately addressed. Discussions regarding product labeling and postmarketing requirements have concluded satisfactorily.

Dosing

Carbaglu (carglumic acid) Tablets will be marketed as 200 mg white elongated dispersable tablets with three score marks. The recommended initial dose is between 100 to 250 mg/kg/day. The total daily dose is divided into two to four doses to be given before meals or feedings. In adult patients, each tablet should be dispersed in a minimum of 2.5 mL of water and ingested immediately either orally or via a nasogastric tube. In pediatric patients, each tablet should be dispersed in 2.5 mL of water to yield a concentration of 80 mg/mL and may be administered with an oral syringe. During acute hyperammonemic episodes, concomitant administration of other ammonia lowering therapies is recommended. Dosing should be titrated based on individual patient plasma ammonia levels and clinical symptoms.

Regulatory History

Carglumic acid received orphan designation in 1998 and was the subject of NDA (b) (4), a rolling submission. The final reviewable unit was submitted on July 11, 2008, and received on July 14, 2008. Upon receiving DGP's preliminary assessment that the deficiencies in the application could preclude filing if not addressed by the filing date, the applicant withdrew the NDA on July 25, 2008. NDA 022562, submitted on June 17, 2009, and received on June 18, 2009, was filed and granted a priority review. A submission dated October 14, 2009, and received on October 15, 2009, was considered a major amendment, and extended the review clock to March 18, 2010. The efficacy and safety of carglumic acid were discussed at a January 13, 2010 meeting of FDA's Endocrinologic and Metabolic Drugs Advisory Committee. Committee members voted 12-0 in favor of approval of the application.

A Form 483 was issued following an inspection conducted (b) (4) (b) (4) the finished dosage manufacturer in (b) (4). Inspectors cited concerns regarding impurities test methods. Upon reviewing (b) (4) response dated November 19, 2009, the Office of Compliance sent additional comments and an information request on February 1, 2010. (b) (4) response dated March 10, 2010 was considered acceptable. A re-inspection of this facility will be conducted approximately one year post-approval.

Efficacy

The efficacy of carglumic acid was assessed using clinical information from 23 patients that was collected retrospectively from chart reviews. Clinical information from three additional patients treated on an ongoing, phase 2 study conducted by Mendel Tuchman at the Children's National Medical Center, Washington, DC, was considered supportive.

The 23 patients received treatment between 1987 and 2008 for a median of 7.9 years (range 0.6-20.8 years) at 14 locations outside the US. Fourteen of these patients had complete NAGS deficiency. The applicant assessed the effect of treatment on plasma ammonia levels both in the short-term (within 3 days of initiation of treatment) and long-term. Plasma ammonia levels were obtained in the course of clinical management of these patients. The applicant retrospectively defined the baseline measurement as the level obtained at the closest time point to the first treatment with carglumic acid. For post-treatment levels, if multiple levels were obtained on the same day, the highest post-treatment level was used. A reduction in the median ammonia level was observed within 24 hours of initiation of carglumic acid, and normalization was observed by day 3 of carglumic acid treatment. Median levels remained normal as of the last available value. The majority of patients assessed in the long-term were on sole therapy with carglumic acid, and had discontinued other available therapies and dietary restriction of protein.

Since plasma glutamine levels are increased in patients with NAGS deficiency, these were also measured. Median plasma glutamine levels appear to decrease on days 1 and 2 and in the long-term (i.e., at the last available measurement on carglumic acid treatment) in evaluable patients.

Only two of 14 patients with complete NAGS deficiency died; one of these had erratic plasma ammonia levels attributable to noncompliance with carglumic acid treatment. A survival rate of 86% in these patients compares favorably with the published experience of Msall et al. Although no pre-specified tools were used, information was available on 17 patients who received periodic neurocognitive assessments while on carglumic acid treatment. Nine of these patients presented with neurologic impairment that improved on treatment, while three patients had normal neurologic function at baseline that remained normal. Thus, at the time of last follow-up, 12 of 17 (71%) evaluable patients had normal neurologic function. At the time of last follow-up, all twelve were on unrestricted protein intake and eight were on carglumic acid as their sole treatment.

In the Tuchman experience, 3 patients with late-onset NAGS deficiency received carglumic acid for a total of 3 days. Plasma ammonia levels decreased in 2 of the 3 patients, however, only one of the patients enrolled had baseline hyperammonemia.

Conclusion. Ammonia has been implicated as a neurotoxin in a variety of disorders, including urea cycle enzyme deficiencies. Prolonged hyperammonemic episodes have been associated with irreversible neurologic impairment and increased mortality. Thus, the effects of carglumic acid in lowering plasma ammonia levels in patients with NAGS deficiency in the short- and long-term are considered important predictors of clinical benefit in these patients.

Safety

Although the number of NAGS deficiency patients treated with carglumic acid is small, 8 patients received treatment for over 10 years, and 6 received treatment for over 5 years but less than 10 years. Treatment was generally well-tolerated.

Two patients with complete NAGS deficiency died; both deaths were unrelated to carglumic acid treatment. Vomiting and somnolence were reported in 6 and 2 patients, respectively. These events are also manifestations of hyperammonemia. The most commonly reported adverse events included events that are common in childhood, such as ear infections, tonsillitis, nasopharyngitis, headache, and diarrhea. Three patients experienced anemia.

Clinical Pharmacology

The proposed starting dose, 100 – 250 mg/kg/day, is based on clinical experience with the use of carglumic acid in 23 patients with NAGS deficiency. Maintenance dosing with less than 100 mg/kg/day appears to provide adequate control of plasma ammonia levels. Given the limited experience in treating this disease, decisions regarding withdrawal of other available therapies and dietary protein restriction will need to continue to be made on a case-by-case basis.

Nonclinical Findings

There are no nonclinical study findings that preclude approval. Carglumic acid was negative in the Ames test, chromosomal aberration assay in human lymphocytes, and the *in vivo* micronucleus assay in rats. A two-year carcinogenicity study will be required post-approval.

The NDA did not include chronic toxicology information in a non-rodent species. Although the DGP pharmacology/toxicology reviewers recommended that this information be obtained post-approval, the Associate Director for Pharmacology/Toxicology advised that these data were not needed. 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. I concur that a post-approval chronic toxicology study in non-rodents is not needed at this time.

Tradename Review

The Division of Medication Error Prevention and Analysis (DMEPA), in consultation with the Division of Drug Marketing, Advertising, and Communications (DDMAC), have concluded that the tradename "Carbaglu" is acceptable.

Pediatric Considerations

Pediatric Use. Carglumic acid will be indicated for the treatment of hyperammonemia in patients with NAGS deficiency from birth to adulthood. The recommended initial dose, 100 to 250 mg/kg/day in 2 to 4 divided doses, is the same in pediatric patients as in adults. For pediatric patients, each tablet should also be dispersed in 2.5 mL of water to yield a concentration of 80 mg/mL and may be administered with an oral syringe.

Required Pediatric Studies. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because this drug product for this indication has an orphan drug designation, the applicant is exempt from this requirement.

Postmarketing Requirements under 505(o)

Section Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious risks of carcinogenicity, or unexpected serious risks related to long-term exposure in patients, including pregnant women and their fetuses.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that Orphan Europe is required to conduct the following studies:

1. a two-year carcinogenicity study in a single rodent species;
2. a registry of patients, including infants, 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 and dietary protein management, clinical status, neurocognitive outcomes, growth and development, and adverse events. Information from this registry will be submitted annually with a final report submission at 15 years post-approval; and
3. 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 will be submitted annually and included in the final report submission on the registry at 15 years post-approval.

Postmarketing Commitments Subject to Reporting Requirements Under Section 506B

Orphan Europe plans to complete and submit the final study report for the on-going study entitled, "*In vitro* metabolic stability of N-carbamyl [^{14}C]-glutamic acid in rat, mini-pig, dog, monkey and human hepatocytes." In addition, the applicant commits to conduct an *in vitro* study to assess the potential for carglumic acid to inhibit or induce cytochrome P450 enzymes.

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CDER, FDA

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/

JULIE G BEITZ
03/18/2010