CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-562

SUMMARY REVIEW

MEMORANDUM

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

DATE: **March 16, 2010**
TO: **Julie Beitz, MD**
Director, Office of Drug Evaluation III

FROM: **Donna Griebel, MD**
Director, Division of Gastroenterology Product

SUBJECT: **Approval Action - NDA 022562 Carbaglu (carglumic acid)**
Oral Tablet 200 mg
Orphan Europe

I concur with the recommendations of the reviewers that NDA 022562 for Carbaglu (carglumic acid) should receive an Approval action for the indication treatment of hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS deficiency). There is no product approved to treat NAGS deficiency in the United States. NAGS deficiency is an extremely disease, with only approximately 50 known cases reported worldwide. Carglumic acid is a structural analogue of N-acetyl-glutamate, the product of NAGS, differing only by the substitution of a terminal ammonia group for the terminal methyl group. N-acetyl-glutamate (NAG) is a cofactor that activates carbamyl phosphate synthetase (CPS), an essential enzyme in the urea cycle.

This application received a priority review designation, and I concur with the clinical reviewers that the retrospective case series summary data submitted in this NDA and the data from 3 patients with NAGS deficiency treated in a prospective trial that investigated the impact of Carbaglu on restoration of ureagenesis provide substantial evidence of efficacy, as defined in Section 505(d) of the Food Drug and Cosmetic Act. Section 505(d) states that substantial evidence consists of "adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof". Although the retrospective case series data submitted in this NDA are not derived from traditionally defined adequate and well controlled investigations, the plasma ammonia level data submitted for review do stand as evidence "on the basis of which it could fairly and responsibly be concluded by experts that the drug will have the effect it purports or is represented to have."

The product is designed to replace a cofactor that is missing in patients with this rare disease. Mechanistically, adequate replacement of a deficient biochemical cofactor of the

urea cycle would yield reduction in elevated plasma ammonia levels. This finding was demonstrated in the aforementioned patients and the reductions in plasma ammonia levels in all patients with available data were both robust and sustained. This evidence was presented to an advisory committee meeting of the Endocrinologic and Metabolic Drugs Advisory Committee on January 13, 2010, and the Committee unanimously voted "yes" that the clinical data included in the Carbaglu application for treatment of hyperammonemia in NAGS deficiency provide substantial evidence of efficacy. They also voted unanimously "yes" that the risk/benefit profile of Carbaglu supports its approval for treatment of hyperammonemia in NAGS deficiency. The Committee members voted that the data support use of Carbaglu for acute episodes of hyperammonemia related to NAGS deficiency (only one member voted "no") and for maintenance treatment of hyperammonemia related to NAGS deficiency (all voted "yes").

The safety database includes 23 patients reviewed as part of the retrospective case series, and seven additional patients treated with Carbaglu as part of the prospective trial evaluating ureagenesis in patients with hyperammonemic disorders. The majority of patients in the retrospective case series were treated with Carbaglu for at least 5 years. The clinical reviewers determined that Carbaglu is well tolerated. There were only two deaths reported in the retrospective case series, and both patient deaths were attributed to their disease and not to treatment with Carbaglu. The most common adverse events reported (in at least 3 patients) were vomiting, abdominal pain, pyrexia, tonsilitis, anemia, ear infection, diarrhea, nasopharyngitis, and headache. The Advisory Committee members stated they believed that Carbaglu may have broader off-label use in other rare disorders after approval of the product (for other forms of urea cycle disorders), and recommended that a patient registry be implemented post-approval to further evaluate the long-term safety of Carbaglu.

The summary findings of the review disciplines are listed below:

CMC – The CMC reviewers have recommended approval of NDA 022562. They concluded the data in the application support that the manufacture of the product is well controlled and yields a pure and potent product. The applicant's proposal for drug product shelf life of 24 months when stored at 5^{o}C was adequately supported.

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 and an exemption for bar code exemption were submitted on March 8, 2010. The Applicant agreed to do 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.

During the inspection of the (b) (4) manufacturing facility for this application, the field investigator conveyed deficiencies to the representative of the facility. The manufacturer provided a response to the deficiencies to the Office of Compliance on November 19, 2009. The responses were insufficient and a letter from the Office of Compliance on February 1, 2010, requested additional information to resolve the deficiencies. The response to the February 1, 2010 letter was reviewed and Office of Compliance determined that there had been satisfactory resolution of the deficiencies.

Pharmacology/Toxicology – The pharmacology reviewers have recommended approval. They concluded that a chronic toxicity study in a non-rodent species should be required as a PMR and that a 2-year carcinogenicity study should be required as a PMR. The applicant stated that the chronic toxicity study in a non-rodent species was not feasible because they cannot produce adequate amounts of the product to achieve appropriate doses for a chronic toxicity in dogs, while still maintaining an adequate supply for patients. They pointed out that the product is currently marketed outside the U.S. and that there are safety data available from that experience that have yielded no concerning safety signals, including in patients who have been dosed for over a decade.

The Associate Director, Dr. A. Jacobs, PhD, entered a memo regarding these nonclinical issues on March 15, 2010. She stated that there are no pharmacology/toxicology issues that preclude approval. She did not concur with the postmarketing studies recommended by the primary and secondary pharmacology reviewers. She stated that there was no need for a chronic study in nonrodents in addition to the rodent chronic study for the following reasons:

1) Human data are sufficient for approval.
2) The animals tested will not have the condition hyperammonemia, and those adverse effects at high doses may not be relevant to the patient population.
3) The drug is lifesaving
4) The number of persons with the condition is small.

She also stated that the carcinogenicity study in a single species was not necessary for similar reasons.

The pharmacology reviewers in DGP do not agree and have concerns that the understanding of potential risks in humans could be optimized by evaluating the histopathology in a nonrodent species. Although I agree that that would be ideal, I do not believe that the study should be required for the reasons Dr. Jacobs stated in her review, and in light of the potential negative impact on drug supply to patients. Additional safety information in humans will be obtained through a postmarketing required study, utilizing a patient registry (see Clinical below).

A 2-year carcinogenicity study in a single species, however, will be required as a PMR pursuant to section 505(0)(3) of the FDCA. The applicant did not indicate that this study would impact drug supply for patients and stated their willingness to perform this study.

Clinical Pharmacology – The clinical pharmacology reviewers have recommended approval.

The reviewers have recommended the following postmarketing commitments (PMCs), and I concur with their recommendations:

1604-4. 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.

1604-5. An *in vitro* study to assess the potential for carglumic acid to inhibit or induce the Cytochrome P450 enzymes.

Clinical – As stated above, the clinical reviewers recommended approval of the Carbaglu for treatment of hyperammonemia secondary to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS deficiency). Of the 23 patients included in the retrospective case series submitted in support of this NDA, 13 patients had complete plasma ammonia level data available. The data in those patients established that Carbaglu treatment was associated with reduction in ammonia levels. As the CDTL, Dr. Lynne Yao, summarizes in her review:

"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. 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). 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."

The following studies will be required as PMRs under section 505(o)(3) of the FDCA:

1. A registry of patients, including infants, with NAGS deficiency being treated with carglumic acid to obtain long-term clinical safety information.

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 for all patients with NAGS deficiency.

Advisory Committee Meeting - This application was discussed at a January 13, 2010 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC). The EMDAC voted unanimously that the clinical data submitted to support the effectiveness of Carbaglu for the proposed indication met the legal standard for substantial evidence. The members noted that the pathophysiology of the disease and the mechanism of action of the drug were well understood. The changes in plasma ammonia levels provided objective evidence of efficacy.

Pediatrics – Carbaglu is an orphan product so the Pediatric Research Equity Act does not apply. Pediatric patient data were included in the retrospective case series submitted in support of this NDA.

Division of Scientific Investigations – No issues precluding approval were identified by DSI.

Division of Medication Error Prevention and Analysis – The DMEPA reviewers found the applicant's proposed proprietary name, Carbaglu, acceptable.

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/

DONNA J GRIEBEL
03/16/2010