

**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Endocrinologic and Metabolic Drugs Advisory Committee Meeting
Hilton Hotel, Silver Spring, Maryland
January 13, 2010**

Questions to the Advisory Committee

The committee will discuss new drug application (NDA) 22-562, CARBAGLU (carglumic acid) Tablets, Orphan Europe, S.A.R.L. The proposed indication of CARBAGLU in this application is for the specific treatment of hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS deficiency).

EFFICACY

1. The legal effectiveness requirement for drug approval is “substantial evidence,” defined as “evidence consisting of adequate and well-controlled investigations, including clinical investigations, ... on the basis of which it could fairly and responsibly be concluded ... that the drug will have the effect it purports or is represented to have” In some cases, substantial evidence may be considered to be “data from one adequate and well-controlled clinical investigation and confirmatory evidence”

Do the clinical data included in the Carbaglu application for treatment of hyperammonemia in NAGS deficiency provide substantial evidence of efficacy?

Vote: Yes/No/Abstain

Discuss the rationale for your vote, and in your discussion please include responses to the following questions:

- A. What clinical data were persuasive?
 - B. What deficiencies in the clinical data make you consider the evidence to be less than substantial?
2. Do the data support the effectiveness of Carbaglu for treatment of **acute** hyperammonemia (i.e., initial treatment and subsequent episodes of acute hyperammonemia) in NAGS deficiency?

Vote: Yes/No/Abstain

Discuss the rationale for your vote, and in your discussion please include responses to the following questions and issues:

- A. What clinical data were persuasive?
- B. If Carbaglu is approved for the treatment of acute hyperammonemia, the product labeling will need to include dosing recommendations for acute treatment. Please provide recommendations that address:
 - Starting dose of Carbaglu (if different from the Applicant’s proposed starting dose of 100-250mg/kg/day in divided doses)

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- Dose adjustments during acute hyperammonemia
 - Use of adjunctive ammonia lowering therapies during acute hyperammonemia
3. Do the data support the effectiveness of Carbaglu for **maintenance** treatment of hyperammonemia in NAGS deficiency?

Vote: Yes/No/Abstain

Discuss the rationale for your vote, and in your discussion please include responses to the following questions and considerations:

- A. What clinical data were persuasive?
- B. If Carbaglu is approved for the maintenance treatment of hyperammonemia, the product labeling will need to include dosing recommendations for maintenance treatment. Please provide recommendations that address:
 - Dose during maintenance treatment
 - Clinical monitoring necessary to guide maintenance dosing (e.g., plasma ammonia level, glutamate level, etc.)
 - Use of adjunctive ammonia lowering therapies during maintenance treatment

SAFETY

4. Based on the overall safety data presented, do you have safety concerns that should be addressed? If so, please describe how these safety concerns should be addressed (i.e., further studies, product labeling, etc.)

Vote: Yes/No/Abstain

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RISK/BENEFIT ASSESSMENT

5. Does the risk/benefit profile of Carbaglu support its approval for treatment of hyperammonemia in NAGS deficiency?

Vote: Yes/No/Abstain

6. What additional studies, if any, should be performed to further evaluate the safety and/or efficacy of Carbaglu in the treatment of hyperammonemia due to NAGS deficiency? Please include in your answer whether these studies should be performed pre-approval or post-approval.