Carbaglu® (Carglumic acid) tablets

Advisory Committee Meeting
FDA Clinical Summary
January 13, 2010

Division of Gastroenterology Products
CDER/FDA

Purpose of Meeting

To consider the evidence available to support the effectiveness and safety of Carbaglu (Carglumic acid) in the treatment of hyperammonemia due to NAGS deficiency.

Level of Evidence: Legal Requirements

- 1962 Drug Amendments to the FDC Act
  - Required establishment of effectiveness of the drug as a prerequisite for marketing approval
  - Effectiveness established by "Substantial Evidence"

What is “Substantial Evidence”?

Section 505(d) of the Act:

“. . .evidence consisting 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.”

Substantial Evidence

- Adequate and well-controlled investigations
  - Quantity
  - Quality
- FDA has been flexible within the limits set by law

Quantity of Evidence

- Generally applied, at least two adequate and well-controlled studies, each convincing on its own
- Limitations of reliance on a single study for substantial evidence
  - Any trial may be subject to unanticipated, undetected, systematic biases
  - Any trial may have a positive finding due to chance alone – a false positive finding
  - Independent substantiation of results helps minimize an erroneous conclusion that a drug is effective

When May a Single Adequate and Well-Controlled Study be Sufficient?

- Generally limited to situations where an adequate and well-controlled trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome AND
- A second adequate and well-controlled trial would be practically or ethically impossible

Quality of Evidence

- "A design that permits a valid comparison with a control to provide a quantitative assessment of drug effect"
- Control group may be concurrent or non-concurrent (historical control)
- Use of Historical Control (21 CFR 314.126 (b.2.v))
  - The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations.
  - Usually reserved for special circumstances
  - Studies of diseases with high and predictable mortality and studies in which the effect of the drug is self-evident (e.g., anesthetics)

Quality of Evidence

- The method of selection of subjects provides adequate assurance that they have the disease or condition being studied
- The method of patient assignment should minimize bias
- Measures should be taken to minimize bias on the part of the subjects, observers, and analysts of the data
- The method should assure comparability of the groups with respect to pertinent variables
- Methods of assessment of subjects' response are well-defined and reliable
- Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness

Orphan Drug Act

- Applies to drugs and biologic products developed for a disorder affecting fewer than 200,000 people in the United States
- Passed in 1983
- Orphan Drug Requirements
  - Demonstrate **substantial evidence of effectiveness or clinical benefit**
  - Does not hold Orphan drug development to a different standard than non-Orphan drugs

Selected Orphan Product Approvals

Drug	**Indication, Year of Approval**	**Basis for Approval (All were based on a single trial)**
Ceredase®	Gaucher Disease, 1991	N=12, Change from baseline for hematologic and organ volume measurements
Cerezyme®	Gaucher Disease, 1994	N=30, R, DB parallel group compared with Ceredase using similar endpoints
Aldurazyme®	MPS I, 2003	N=45, R, DB, PC; change in 6MWT and FVC (co-primary)
Elaprase®	MPS II, 2006	N=96, R, DB, PC; change in 6MWT and FVC (composite primary)
Naglazyme®	MPS VI, 2005	N=39, R, DB, PC; change in 12MWT
Fabrazyme®	Fabry Disease, 2003	N=58, R, DB, PC; clearance of GL-3 from kidney interstitial capillaries (Subpart E approval)
Myozyme®	Pompe Disease, 2006	N=18, Open label, Historically controlled; change in ventilator-free survival

Basis of Approval Ammonul

Drug	Indication	Basis for Approval in 2005
Ammonul®	adjunctive therapy for the treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle.	N=316 Open label, Historically controlled Primary endpoint: overall survival (80% overall vs. 48% in historical control group)

Carbaglu (Carglumic acid) NDA 22-562

- Proposed indication:
  - Hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS deficiency)

Studies used in support of NDA 22-562

- Retrospective case series in 23 patients with NAGS deficiency treated with Carbaglu over 21 years

- Prospective, open-label study in 3 patients with NAGS deficiency treated with Carbaglu for 3 days

Question 1

- Do the clinical data included in the Carbaglu application for treatment of hyperammonemia in NAGS deficiency provide substantial evidence of efficacy?
- Discuss the rationale for your vote, and in your discussion please include responses to the following questions:
  - What clinical data were persuasive?
  - What deficiencies in the clinical data make you consider the evidence to be less than substantial?

Question 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?
- Discuss the rationale for your vote, and in your discussion please include responses to the following questions and issues:
  - What clinical data were persuasive?
  - 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)
    - Dose adjustments during acute hyperammonemia
    - Use of adjunctive ammonia lowering therapies during acute hyperammonemia

Question 3

- Do the data support the effectiveness of Carbaglu for maintenance treatment of hyperammonemia in NAGS deficiency?
- Discuss the rationale for your vote, and in your discussion please include responses to the following questions and considerations:
  - What clinical data were persuasive?
  - 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

Question 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.)

Question 5

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

Question 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.

Basis for Approval of Ceredase

ERT	Indication	Basis for Approval in 1991
Ceredase® (alglucerase)	Gaucher Disease	N=12 Duration = 9 months Ages = 7-42 years[1] Endpoint = Change from baseline at 6 months in hematologic and organ volume measurements. Results: • Hgb ↑ in 12/12 ($p<0.003$) • Plt ↑ in 7/12 (p values ranged from 0.0001-0.026) • Liver volume ↓ in 5/12 (16-22%) • Spleen volume ↓ in 12/12 (14-75%)

[1] Barton NW, Brady RO, Dambrosia JM et al. Replacement therapy for inherited enzyme deficiency – macrophage-targeted glucocerebrosidase for Gaucher's disease. N Engl J Med 1991;324:1264-70.

Basis for Approval of Cerezyme

ERT	Indication	Basis for Approval in 1994
Cerezyme® (imiglucerase)	Gaucher Disease	N=30 Single R, DB, parallel group study comparing PK and PD of Cerezyme and Ceredase.[2] Duration = 9 months Endpoints = Mean change from Baseline at 9 months in hematology and organ volumes: • Hgb ↑23-25% • Plt count ↑ 44-53% • Liver volume ↓ 16-21% • Spleen volume ↓ 42-27% No significant differences observed between the two groups for any parameter (p>0.2).

[2] Grabowski GA, Barton NW, Pastores G et al. Enzyme therapy in type 1 Gaucher disease: Comparative efficacy of mannose-terminated glucocerebrosidase form natural and recombinant sources. Ann Intern Med 1995;122:33-39.

Basis for Approval of Myozyme

ERT	Indication	Basis for Approval in 2006
Myozyme®	Pompe Disease	N=18 Single Phase 3, Open Label, Historically-controlled Population = Infantile-onset Pompe patients Duration = 52 weeks Age = <7 months at first infusion. Primary endpoint: • Death or requiring invasive ventilatory support at 18 months of age Myozyme group 17% (95% CI 4-41%) vs. 98% in historical control group.

Bias

- Deviation of results or inferences from the truth, or processes leading to such systematic deviation; any trend in the collection, analysis, interpretation, publication, or review of data that can lead to conclusions that are systematically incorrect*
- *Selection bias*
  - related to the way people are recruited or retained during the course of the study
- *Information bias*
  - related to the way the information is measured or obtained during the study
- *Confounding*
  - related to the influence of other variables that are related to both drug use and the outcome, and may be responsible for part or all of the observed effect, the lack of observed effect, or a reversal of the effect.

*McGraw-Hill Concise Dictionary of Modern Medicine. © 2002 by The McGraw-Hill Companies, Inc.

Minimizing Bias

- Minimizing Selection Bias
  - Randomization
  - Systematic Recruitment
  - Well-codified accrual of patients (based on nature and severity of the disease)
  - Minimizing patient drop out
- Minimizing Information Bias
  - Blinding
  - Standardization of the measurement process
- Controlling for Confounding
  - Randomization
  - Matching
  - Restriction