



# **Zavesca<sup>®</sup> (Miglustat) Capsules**

## **Advisory Committee Meeting FDA Clinical Summary January 12, 2010**

**Division of Gastroenterology Products  
CDER/FDA**

# 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**
  - Plural vs. Single trial?
  - What is Adequate and Well-Controlled?
- **...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.

# How Many Studies?

- Generally applied, at least two adequate and well-controlled studies, each convincing on its own.
- Broadly interpreted to the extent possible
- FDAMA 1997 (amended 505(d) of the Act)
  - Made clear that may consider data from one adequate and well controlled investigation and confirmatory evidence to constitute substantial evidence, if the FDA determines the data and evidence are sufficient to establish effectiveness
  - If a single adequate and well-controlled study, the submitted study is held to a higher standard

# Limitations of Reliance on a Single Trial 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

# What is an Adequate and Well-Controlled Trial?

- (21 CFR 314.126): “A design that permits a valid comparison with a control to provide a quantitative assessment of drug effect”
- Components to assess to determine if trial is adequate and well controlled
  - Type of control
  - Assignment of subjects
  - Adequacy of bias minimization

# Choice of Control: Historical Controls

- 21 CFR 314.126 (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.**

# Historical Controls (21 CFR 314.126)

- 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 (eg. anesthetics)

# Adequate and Well-Controlled: Methodology for Treatment Group Assignment (21 CFR 314.126 (b))

- The method should minimize bias
- The method should assure comparability of the groups with respect to pertinent variables
- Types of bias include
  - *Selection bias* = related to method of recruitment or retention
  - *Information bias* = related to the way the information is measured or obtained during the study
  - *Recall bias* = important concern in retrospective studies where cases and controls may have a different memory/record of past experience
  - *Detection bias* = when the procedures for assessment are not similar in cases and controls

# Minimizing Bias

- Adequate measures should be taken to minimize bias on the part of
  - Subjects
  - Observers
  - Analysts of the data
- Examples of procedures used to accomplish this
  - Randomization
  - Double-blinding

# Issues in Minimization of Bias

- Reliance on subjective measurements in the context of an open label study or a study in which there is limited ability to blind
- Retrospective chart reviews

# What is the Legal Standard for “Substantial Evidence” in Treatments for Rare Diseases?

Section 505(d) of the Food and Drug 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.”

# Orphan Drug Act

- Applies to drugs and biologic products developed for disorders affecting fewer than 200,000 people in the U.S.
- Passed in 1983
- Orphan Drugs must
  - 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

<b>Drug</b>	<b>Indication, Year</b>	<b>Basis for Approval</b>
Ceredase®	Gaucher Disease, 1991	N=12, Change from baseline for heme/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)
Myozyme®	Pompe Disease, 2006	N=18, Open label, Historically controlled; change in ventilator-free survival
Ammonul®	Hyperammonemia, 2005	N=316, Open label, Historically controlled; overall <sub>16</sub> survival

# Zavesca (miglustat) NDA 21384

- Proposed Indication:
  - for the treatment of progressive neurological manifestations in adult and pediatric patients with Niemann-Pick type C disease (NP-C).

# Collective Evidence in sNDA 21384

- Study 007 – Major Study
  - Controlled, Unblinded
  - Followed by an uncontrolled extension
- Survey 1
  - Retrospective chart review, uncontrolled
- Survey 2
  - Retrospective chart review, uncontrolled
- Case Studies
  - Retrospective

# Question 1

In drug development plans for products to treat Niemann-Pick type C (NP-C), which endpoint(s) should be evaluated to establish clinical benefit?

## Question 2

Do you consider that the clinical data included in the Zavesca application for NP-C provide substantial evidence of efficacy?

In your response, please also discuss your thinking regarding the following issues:

## Question 2

- Which clinical data (studies & endpoints), if any, provide the substantial evidence of efficacy?
- What, if any, are the deficiencies in the clinical data that make the evidence less than substantial?
- What, if any, specific clinical benefit(s) were established (indication for labeling)?

## Question 3

Does this application raise concerns about the adequacy of the safety assessments or the safety findings for Zavesca at the proposed dose in NP-C patients?

If so, what are those concerns, and how should they be addressed (e.g., studies, analyses, labeling)?

## Question 4

- In light of the safety and efficacy data presented in this application, does the risk/benefit profile of Zavesca support its approval for treatment of NP-C?

# Question 5

Are there any additional studies that need to be conducted?



# Basis for Approval of Ceredase

ERT	Indication	Basis for Approval in 1991
Ceredase® (alglucerase)	Gaucher Disease	<p>N=12 Duration = 9 months Ages = 7-42 years<sup>1</sup> Endpoint = Change from baseline at 6 months in hematologic and organ volume measurements. Results:</p> <ul style="list-style-type: none"> <li>• Hgb ↑ in 12/12 (p&lt;0.003)</li> <li>• Plt ↑ in 7/12 (p values ranged from 0.0001-0.026)</li> <li>• Liver volume ↓ in 5/12 (16-22%)</li> <li>• Spleen volume ↓ in 12/12 (14-75%)</li> </ul>

<sup>1</sup> 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	<p>N=30</p> <p>Single R, DB, parallel group study comparing PK and PD of Cerezyme and Ceredase.<sup>2</sup></p> <p>Duration = 9 months</p> <p>Endpoints = Mean change from Baseline at 9 months in hematology and organ volumes:</p> <ul style="list-style-type: none"> <li>• Hgb ↑23-25%</li> <li>• Plt count ↑ 44-53%</li> <li>• Liver volume ↓ 16-21%</li> <li>• Spleen volume ↓ 42-27%</li> </ul> <p>No significant differences observed between the two groups for any parameter (p&gt;0.2).</p>

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

# Basis for Approval of MPS I, II, VI ERTs

ERT	Indication	Basis for Approval in 2003, 2006 and 2005
Aldurazyme® (laronidase)  2003	MPS I	N=45 Single Phase 3, R, DB, Placebo Control study Duration = 53 weeks      Age = 6-43 years. Co-primary endpoints • 6MWT: +38 m, p=0.07 (Wilcoxon Rank Sum Test) • FVC (% predicted): +4%, p=0.02
Elaprase® (idursulfase)  2006	MPS II	N=96 Single Phase 3, R, DB, Placebo Control study Duration = 26 weeks      Age = 5-31 years. Composite primary endpoint, p=0.0049 (Rank Sum) • 6MWT: +35 m, p=0.01 (ANCOVA) • FVC: +4%, p=0.07
Naglazyme® (galsulfase)  2005	MPS IV	N= 39 Single Phase 3, R, DB, Placebo Control study Duration = 24 week      Age = 5-29 years. Primary endpoint: • 12MWT: +92 m, p=0.025 (model-based mean) Secondary endpoint: • 3-minute stair climb (stairs/minute): +6, p=0.053

# Basis for Approval of Fabrazyme

ERT	Indication	Basis for Approval in 2003
<p>Fabrazyme® (agalsidase beta)</p>	<p>Fabry Disease</p>	<p><b>Accelerated Approval (Subpart E):</b>                      N=58                      Single Phase 3, R, DB, Placebo Control study                      Duration = 20 weeks                      Ages= 16 - 61 years.                      Primary endpoint = GL-3 (enzyme substrate) clearance from interstitial capillary endothelial cells, graded 0 (normal) to 3 (severe) inclusions.</p> <ul style="list-style-type: none"> <li>• GL-3 score of 0 achieved in 69% of Fabrazyme-treated vs. 0 patients treated with placebo, p&lt;0.001.</li> </ul> <p><b>Condition of Approval</b> = Conduct a Phase 4, R, DB, PC study to verify and describe clinical benefit – assessing significant clinical events.</p>

# Basis for Approval of Myozyme

ERT	Indication	Basis for Approval in 2006
Myozyme®	Pompe Disease	<p>N=18            Single Phase 3, Open Label, Historically-controlled            Population = Infantile-onset Pompe patients            Duration = 52 weeks            Age = &lt;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.</p>

# Basis of Approval Ammonul

<b>Drug</b>	<b>Indication</b>	<b>Basis for Approval in 2005</b>
Ammonul®	adjunctive therapy for the treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle.	N=316 Single Phase 3, Prospective, Open label, Historically controlled Primary endpoint: survival (80% overall vs. 48% in historical control group)