Orphan Medicinal Products in the USA: Current Marketing Authorisations for Gaucher Disease

Carla Epps, MD, MPH, FAAP
Division of Gastroenterology & Inborn Errors Products
Food & Drug Administration
September 17, 2012

Gaucher Orphan Product Designations

- **14** orphan designations granted
- **4** approved & currently marketed products
  - 3 enzyme replacement therapy (ERT) products
  - 1 substrate reduction therapy (SRT) product
- **No** current active orphan product grants

Gaucher Products with Orphan Designation

ERT Products	SRT Products	Pharmacological Chaperones	Other
•Alglucerase •PEG-glucocerebrosidase •Recombinant glucocerebrosidase •Imiglucerase •Velaglucerase •Taliglucerase	•L-cycloserine •Miglustat •Eliglustat	•Isofagamine •Ambroxol	•Alendronate

ERT= Enzyme Replacement Therapy
SRT= Substrate Reduction Therapy

US-Approved Products for Gaucher Disease

Name	Product Class	Indication
Ceredase (alglucerase)*	ERT	Gaucher Type 1
Cerezyme (imiglucerase)	ERT	Gaucher Type 1
VPRIV (velaglucerase alfa)	ERT	Gaucher Type 1
Elelyso (taliglucerase alfa)	ERT	Gaucher Type 1 (adults only)
Zavesca (miglustat)	SRT	Gaucher Type 1 when ERT is not an option (adults only)

*discontinued from market

ERT= Enzyme Replacement Therapy
SRT= Substrate Reduction Therapy

US-Approved Gaucher Products: Trial Design

Product	Population	Design	Endpoints
Alglucerase (Ceredase)	Treatment-naïve	OL, single arm, historical control	Change in hemoglobin, platelet count, liver, spleen
Imiglucerase (Cerezyme)	Treatment-naïve	Randomized, DB, active control (Ceredase)	Change in hemoglobin, platelet count, liver, spleen
Miglustat (Zavesca)	Treatment-naïve Patients not receiving ERT	2 trials: both OL, single arm, historical control Randomized, OL, active control (Cerezyme), 3-arm	Change in hemoglobin, platelet count, liver, spleen

US-Approved Gaucher Products: Trial Design

Product	Population	Design	Study Endpoints
Velaglucerase (VPRIV)	Treatment-naïve Treatment-naïve ERT-treated patients	Randomized, DB, parallel dose Randomized, DB, active control (Cerezyme) OL, single-arm, historical control, switch from prior ERT	Change in hemoglobin, platelet count, liver, spleen
Taliglucerase (Elelyso)	Treatment-naïve ERT-treated patients	R, DB, parallel dose OL, single-arm, historical control, switch from prior ERT	Change in hemoglobin, platelet count, liver, spleen

Gaucher Trial Endpoints

- Disease course is evolving with development of ERT and other therapies
  - Earlier ERT trials initially focused on biomarkers, hematologic and visceral organ endpoints
  - Elelyso trials used responder analyses of hematologic and visceral disease
  - Bone disease also assessed in some trials
    - State of art for assessing bone disease is evolving

US-Approved Gaucher Products: Indications

- 5 products are approved; 4 products are still commercially available
  - 2 products indicated for pediatric use
  - No US products specifically indicated for treatment of neuronopathic Gaucher disease

Pediatric Labeling for Gaucher Products

- **Ceredase/Cerezyme**

"The **safety and effectiveness** [of Ceredase and Cerezyme] have been **established in patients between 2 and 16 years of age**. Use …in this age group is **supported by evidence from adequate and well-controlled studies** of [Ceredase and Cerezyme] in adults and pediatric patients, with additional data obtained from the medical literature and from longterm postmarketing experience."

- **Zavesca**

"The **safety and effectiveness** of Zavesca in pediatric patients **have not been established**."

Pediatric Labeling for Gaucher Products

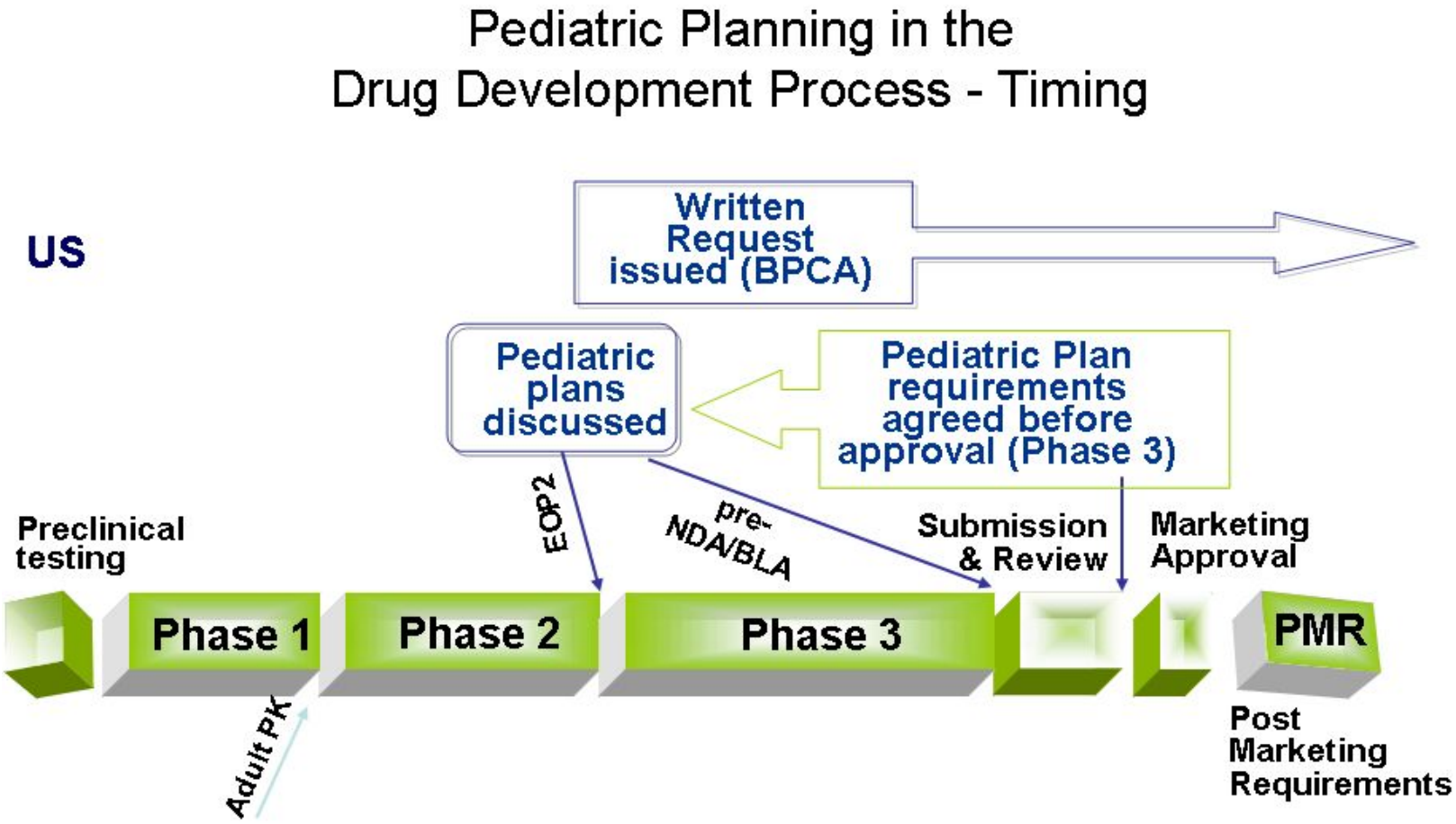
- **VPRIV**

"The **safety and effectiveness** of VPRIV have been **established in patients between 4 and 17 years of age**. Use of VPRIV in this age group is **supported by evidence from adequate and well-controlled studies** of VPRIV in adults and pediatric [20 of 94 (21%)] patients."

- **Elelyso**

"The **safety and effectiveness** of ELELYSO in pediatric patients **have not been established**. "

US Pediatric Planning Process



Pediatric Clinical Development Issues

- Limited number of pediatric patients available for enrollment
- Trial design and study endpoints, especially for non-ERT products
- PREA exemption for orphan products
  - implications for timing of development of pediatric plans
- BPCA provides incentives for development
  - legislation now permanent under FDASIA