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Drug Class Review: Targeted Therapies for Gaucher Disease

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Purpose for Class Review: To evaluate evidence of efficacy and safety for current pharmacological treatments for Gaucher Disease.

Research Questions:

1. What is the efficacy or effectiveness of pharmacological treatments for Gaucher Disease compared to placebo or other pharmacotherapy?
2. Is there any evidence that pharmacological treatments for Gaucher Disease differ in harms?
3. Are there specific subpopulations for which one agent is better tolerated or more effective than other therapies?

Conclusions:

- There is low quality evidence of no difference in hemoglobin concentration, platelet count, liver volume or spleen volume for imiglucerase compared to velaglucerase alfa in patients with symptomatic Type 1 Gaucher disease.[1,2] Evidence is limited by small study populations, lack of comparator groups, and open-label study designs.[1,2]
- There is insufficient direct comparative evidence for taliglucerase alfa, but placebo comparisons demonstrate improvements in hemoglobin levels (MD 1.4 to 2.2 g/dL), spleen volume (MD -27% to -41%), and liver volume (MD -6.3% to -4.1%) with inconsistent evidence for improved platelet counts.[3] It is unclear whether these differences correlate with improved clinical outcomes for patients with Type 1 Gaucher disease, and there are insufficient data from RCTs on long-term outcomes including quality of life, disease progression, or mortality.
- There is low quality evidence from a single non-inferiority trial that patients switching from imiglucerase to eliglustat maintain disease stability compared to continued treatment with imiglucerase (84.8% vs. 93.6%, respectively).[4] Compared to placebo at 39 weeks, there was low quality evidence of statistically significant differences with eliglustat treatment in all laboratory markers including reduction in spleen volume (mean difference [MD] 30%, 95% CI 36.82 to 23.24; p<0.001), liver volume (MD −6.64%, 95% CI −11.37 to −1.91; p=0.0072), hemoglobin level (MD 1.22 g/dL, 95% CI 0.57 to 1.88; p=0.0006), and platelet count (MD 41.06%, 95% CI 23.95 to 58.17; p<0.0001), but no differences in bone disease or symptom improvement at 39 weeks.[4] Eliglustat is primarily metabolized by P450 enzymes and requires CYP2D6 testing to determine metabolizer status and appropriate dose.[5]
- Trials evaluating miglustat and imiglucerase as monotherapy or combination therapy demonstrated no difference in laboratory markers in patients previously stable on enzyme replacement therapy (ERT).[1,2] Food and Drug Administration (FDA) labeling for miglustat recommends it as a second-line option only for patients who are unable to receive ERT.[6]
- There is insufficient data from RCTs to evaluate clinical bone-related outcomes, mortality, or quality of life in patients with Type 1 Gaucher disease.
- There is insufficient evidence to support combination treatment with targeted therapies for Gaucher disease.
- There is insufficient evidence of efficacy or safety in patients with Type 2 or Type 3 Gaucher disease.

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Recommendations:

- Create a class for lysosomal storage disorders and designate miglustat as non-preferred based on FDA labeling as second-line therapy and eliglustat as non-preferred based on need for additional enzymatic testing.
- Designate at least one ERT for Gaucher disease as a preferred product. Evaluate comparative costs in executive session.
- Recommend prior authorization criteria for all targeted therapies for Gaucher disease to ensure medically appropriate use.

Background:

Gaucher disease is an inherited, autosomal recessive lysosomal storage disorder. Affected patients have homozygous mutations in the glucocerebrosidase gene (GBA).[7] Over 200 mutations in the GBA gene have been documented, though not all mutations are associated with severe disease or a clinical phenotype. While genotype does not directly correlate to a clinical phenotype, the most common variants include N370S alleles which are associated more commonly with bone involvement and a homozygous L444P genotype which is usually associated with more severe neurologic disease.[7] Mutations in GBA lead to a nonfunctional GBA enzyme and accumulation of glucosylceramide in macrophage cells.[7] These cells, referred to as Gaucher cells, can infiltrate organs including the bone, spleen, and liver leading to displacement of normal cells in the bone marrow, bone marrow expansion, altered vascularity, and tissue death or necrosis.[7] In other tissues, Gaucher cells can cause fibrosis, necrosis, and scarring. Approximately 5% of patients also exhibit neurologic impairment, though the exact etiology for central nervous system (CNS) involvement is unknown.[7]

The rate of disease progression is highly variable, and diagnosis can occur at any age. The disease is classified into primarily 3 types based on clinical presentation. Type 1 is characterized by bone disease and lack of neurologic involvement and accounts for more than 90% of patients.[2,7] Type 2 is associated with severe CNS symptoms and is typically associated with early disease onset, rapid progression, and death by the age of 4 years.[7] The Type 3 is associated with both bone and CNS involvement and is typically less severe than Type 2.[7] Common signs and symptoms of bone involvement include splenomegaly, hepatomegaly, bone pain, radiologic bone disease, growth retardation, thrombocytopenia, and anemia.[2,7] Neurologic symptoms can manifest as a wide variety of symptoms. In patients with Type 2 disease, typical neurologic symptoms include neck and trunk rigidity, oculomotor paralysis, and bulbar involvement (particularly swallowing disorders).[7] Other neurologic symptoms may include progressive myoclonic epilepsy, ataxia, spasticity, delayed psychomotor development, or dementia.[7] Build-up of Gaucher cells in tissue eventually may lead to irreversible fibrosis in the lung, spleen, liver, bone or other tissues. Long-term complications may include osteoarthritis, bone fractures, liver fibrosis, neurologic complications, splenic infarct or rupture, and pulmonary fibrosis.[7] Patients with Gaucher disease also have a higher risk of cancer, particularly multiple myeloma, and Parkinson's disease compared to the general population.[2,7]

Diagnosis of Gaucher disease is typically confirmed by biochemical testing for GBA enzyme activity though molecular genetic testing may be performed to confirm the diagnosis or for prenatal and carrier testing.[7] The estimated prevalence of Gaucher disease is approximately 1 in 40,000 to 60,000 births in the general population, but incidence is much more common in people of Ashkenazi Jewish descent.[2,7] In Oregon, newborn screening currently includes testing for enzymatic activity of GBA, and Gaucher disease is listed on Line 60 of the Health Evidence Review Commission prioritized list. In the Oregon Health Plan (OHP) fee-for service (FFS) population, only one or two patients have claims indicating a diagnosis of Gaucher disease.

Pharmacological treatment is the current standard of care for all patients with symptomatic Type 1 Gaucher disease.[7] The first treatments for Gaucher disease (alglucerase and imiglucerase) were FDA approved in 1991, and currently available therapies include intravenous ERT or oral substrate reduction therapies (**Table 1**). In asymptomatic patients, ongoing monitoring is recommended, and molecular screening may help predict clinical course and inform frequency of monitoring. Because administered ERT does not cross the blood brain barrier, there is little impact on neurologic manifestations of Gaucher disease, and the

limited available evidence does not demonstrate any consistent benefit for patients with neurologic symptoms. Therefore, therapy for Type 2 Gaucher disease is primarily focused on supportive care, and the role of pharmacological treatment in Type 3 disease is unclear.[2,7]

Table 1. Indications and Dosing.[8]

Generic Name (Brand)	Indication(s)	Strength/Route	Dose and Frequency
Enzyme Replacement Therapies			
Imiglucerase (Cerezyme®)	Type 1 Gaucher disease complicated by anemia, thrombocytopenia, bone disease, hepatomegaly, or splenomegaly	400 units IV powder for solution	Initial dosages of 2.5 units/kg 3 times weekly to 60 units/kg once every 2 weeks. Infused over 1-2 hours with dosage individualized to each patient.
Taliglucerase alfa (Elelyso®)	Type 1 Gaucher disease	200 units IV powder for solution	60 units/kg over 1-2 hours every 2 weeks
Velaglucerase alfa (Vpriv®)	Type 1 Gaucher disease	400 units IV powder for solution	60 units/kg over 1 hour every 2 weeks
Substrate Reduction Therapies			
Eliglustat (Cerdelga)	Type 1 Gaucher disease in adults who are not ultra-rapid CYP2D6 metabolizers as detected by an FDA-cleared test	84 mg oral capsule	84 mg BID (extensive or intermediate CYP2D6 metabolizers) 84 mg QD (poor CYP2D6 metabolizers)
Miglustat (Zavesca®)	Mild/moderate Type 1 Gaucher disease in adults for whom ERT is not an option (monotherapy only)	100 mg oral capsule	100 mg TID

Abbreviations: BID = twice daily; ERT = enzyme replacement therapy; FDA = Food and Drug Administration; IV = intravenous; QD = once daily; TID = three times daily

Clinically relevant outcomes for patients with Gaucher disease include symptom improvement (particularly bone pain and fatigue), improved health-related quality of life, slowed disease progression, and prevention of long-term complications such as clinical bone-related events (e.g., bone crisis, fractures, and ischemic bone events), Parkinson's disease and cancer.[9] However, clinical trials primarily focus on assessments of spleen and liver volume, platelet count and hemoglobin level. While hepatomegaly and splenomegaly are often associated with pathologic disease, there is no minimum difference in size which is associated with symptom improvement. In 2018, the European Working Group on Gaucher disease conducted a literature review and a patient survey to assist in the establishment of more specific short and long-term treatment goals.[9] Due to the rarity of the condition, there is limited evidence available on specific goals of treatment, and the majority of recommendations were made were based on expert consensus opinion from 35 providers.[9] Short-term treatment goals for objective laboratory markers which achieved consensus from experts are listed in **Table 2**, though the recommendations are limited as the majority of voting participants had conflicts of interest from industry which may increases risk of bias.[9] General recommendations were also made to improve quality of life, fatigue, function, and bone pain with assessments from validated scoring tools. No consensus was reached on treatment goals for other disease biomarkers or disease severity scores due to insufficient evidence and inadequate validation of these surrogate outcomes.[9]

Current data from RCTs evaluating pharmacological treatment are limited to durations of one to two years, though extension studies have demonstrated continued stability of spleen and liver volume, platelet count and hemoglobin level after 2 to 5 years of treatment in patients with Type 1 Gaucher disease.[5,6,10,11] While there are multiple long-term analyses of international registry and observational studies which evaluate efficacy outcomes before and after the introduction of ERT, the long-term impact of pharmacological therapy on disease progression or long-term complications remains unclear due to methodological limitations in the available observational data and lack of consistently documented disease progression before the availability of ERT.[12,4]

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions.

Table 2. Select short-term treatment goals for patients with Type 1 Gaucher disease based on expert consensus opinion (modified)[9]

Category	Management Goal
Hemoglobin	Increase hemoglobin levels within 12 to 24 months to >11.0 g/dL for women and children and >12.0 g/dL for men
Platelet Count	Increase platelet counts during the first year of treatment sufficiently to prevent surgical, obstetrical, and spontaneous bleeding - In patients with splenectomy: normalization of platelet count by 1 year of treatment - In patients with an intact spleen: achieve platelet count of ≥100,000/mm3 by 3 years of treatment
Bone Mineral Density	Increase bone mineral density by 2 years in adults for patients with a T-score below −2.5 at baseline Attain normal or ideal peak skeletal mass in children Normalize growth such that the height of the patient is in line with target height, based upon population standards and parental height, within 2 years of treatment
Splenomegaly	Reduce spleen volume to <2 to 8 times normal (or in absence of volume measurement tools reduce spleen size) by year 1–2, depending on baseline spleen volume
Hepatomegaly	Reduce the liver volume to 1.0 to 1.5 times normal (or in absence of volume measurement tools aim for normal liver size) by year 1–2, depending on baseline liver volume

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
A Cochrane review published in 2015 evaluated the evidence of safety and efficacy for pharmacologic treatments for Gaucher disease.[2] Four included trials evaluated treatment naïve patients and 4 trials evaluated switching therapy in patients already on treatment.[2] The majority of included studies included adults with average ages ranging from 25 to over 50 years. Three studies included children though the total included population was small. Patients with stable disease were defined as having received ERT for at least 2 years. Five of the 8 included studies had high or unclear risk for selection or performance bias due to inadequate randomization, allocation concealment, or blinding.[2] Two trials had incomplete outcome reporting.[2] Comparisons included same drug dose-comparisons, imiglucerase versus aliglucerase, imiglucerase versus velaglucerase alfa, and imiglucerase versus miglustat. Trial durations ranged from 6 to 24 months.[2] The primary outcome was frequency of adverse events, and safety assessment for ERT included 234 patients.[2] Many common adverse events were classified as infusion-related and were mild, moderate, or transient. Serious adverse events were reported in 19 patients treated with imiglucerase (primarily

associated with worsening disease progression), 3 patients treated with velaglucerase alfa (allergic dermatitis, prolonged aPTT, and seizure), and 2 patients treated with taliglucerase alfa (hypersensitivity reactions).[2] In treatment naïve patients, there was no statistical difference in hemoglobin concentration, platelet count, liver volume, or spleen volume for various ERT products.[2] There was also no difference in treatment outcomes based on dose or frequency for patients with a history of stable disease when evaluating different dosing regimens of velaglucerase alfa, taliglucerase alfa, or imiglucerase.[2] There was insufficient data to evaluate bone-related outcomes for ERT. Two studies evaluated miglustat in combination with ERT compared to monotherapy in patients with Type 1 (n=36) or Type 3 (n=30) Gaucher disease.[2] The most common adverse events associated with treatment were gastrointestinal, weight loss, and neurological.[2] Severe adverse events and withdrawals due to adverse events were not consistently reported for miglustat, but in Type 3 patients, adverse events were severe enough to necessitate prescription of additional therapy in 30% of patients.[2] There was no difference in hemoglobin concentration, liver or spleen volume between miglustat, imiglucerase, or combination treatment for patients with Type 1 Gaucher disease.[2] Platelet count was statistically improved with patients maintained on imiglucerase treatment compared to patients switched to miglustat (20%, p=0.035).[2] For Type 3 patients, there was no apparent difference in hemoglobin concentration, platelet count, and only slight decreases in liver volume or spleen volume after 12 months of treatment with imiglucerase, miglustat or combination therapy (statistical significance not reported).[2] Only 4 patients in miglustat trials experienced bone related outcomes, and there was insufficient evidence to evaluate differences in these outcomes.[2]

A 2011 CADTH report evaluated the efficacy and safety of treatments including eliglustat, miglustat, imiglucerase and velaglucerase for Gaucher Disease.[1] However because this review was published in 2011, the majority of evidence focused on imiglucerase.[1] Overall evidence was of poor quality with substantial evidence from observational studies.[1] Included RCTs were limited by open-label study designs, small sample sizes, short study durations, and poor reporting of randomization and allocation concealment methods.[1] Evidence for imiglucerase primarily reported symptom improvement, and there was only limited data on mortality, quality of life, or long-term skeletal outcomes.[1] One of the included systematic reviews evaluating imiglucerase documented improved bone marrow involvement over 49 months of treatment, but no statistical difference in lumbar spine or femoral bone mineral density Z-scores from baseline.[1] A single, double-blind, non-inferiority RCT (n=34) comparing velaglucerase alfa to imiglucerase, demonstrated comparable hemoglobin levels, liver volume, spleen volume, and platelet counts with both treatments.[1] Three serious adverse events occurred in patients given velaglucerase (seizure, allergic dermatitis, and severe prolonged activated partial thromboplastin time [aPTT]) compared to no events in patients given imiglucerase.[1] Two small trials compared combination treatment with miglustat and imiglucerase compared to imiglucerase alone. Neither trial reported symptom improvement, quality of life, or long-term clinical outcomes, nor was there any difference in hemoglobin level or spleen volume with combination treatment for either study.[1] Evidence was conflicting for platelet count and liver volumes with one trial reporting improvements in liver volume with combination therapy compared to imiglucerase alone (MD 8.5%; p=0.047), but improved platelet count with imiglucerase compared to miglustat (MD 12.6x10^9/L; p=0.035).[1] Overall, authors concluded that there is limited evidence supporting use of ERT with imiglucerase or velaglucerase for Type 1 Gaucher disease, but insufficient data for combination treatment with any agent, and insufficient data for use of substrate reduction therapy.[1]

A third CADTH report evaluating evidence for taliglucerase alfa published in 2015 included 4 studies.[3] Like other drugs, evidence was limited by open-label study designs, lack of comparator groups, small patient populations, lack of intention-to-treat analysis with high attrition rate (29%) in one study, and short study durations (9-12 months).[3] Taliglucerase alfa treatment was evaluated in treatment naïve patients (n=44) and patients with prior imiglucerase use (n=92).[3] In treatment naïve patients, there were statistically significant improvements from baseline in hemoglobin levels (MD 1.4 to 2.2 g/dL), spleen volume (MD -27% to -41%), and liver volume (MD -6.3% to -14.1%).[3] Platelet count was statistically significant from baseline for 60 U/kg (MD 41,494 to 72,600/mm^3) but evidence for 30 U/kg demonstrated inconsistent benefit between studies.[3] In pediatric patients (n=5), the mean change from baseline in height ranged from 4.2 to 7.6% with changes in weight of 9.6 to 14.7% over 9-12 months.[3] There was insufficient evidence to assess quality of life or bone related outcomes, and changes in z-scores, t-scores, and bone mineral density were less than 0.7 for all bone sites indicating little difference over time.[3] No serious adverse events were documented in

treatment naïve patients, but 3-11% of patients switching therapy from imiglucerase had at least one serious adverse event.[3] Of the 4 included studies, 0% (2 studies), 3.4%, and 6.3% of patients withdrew due to adverse events.[3] Overall authors concluded that there was insufficient comparative evidence for taliglucerase alfa and insufficient evidence to evaluate clinically relevant outcomes such as bone crises.[3]

A review of eliglustat for treatment of Type 1 Gaucher disease was published in 2017 from NICE.[4] Eliglustat was recommended within its marketing authorization as an option for treatment of Type 1 Gaucher disease (only when discounts were provided by the manufacturer). This recommendation were primarily based on an analysis of 2 RCTs (comparing eliglustat to placebo or imiglucerase) with supplementary data from a dose comparison study, and a single-arm open-label, phase 2 study.[4] Comparison to imiglucerase was performed in an open-label, non-inferiority trial of patients on ERT with stable disease (n=160).[4] The primary outcome was patients who maintained stable disease for 52 weeks with a non-inferiority margin pre-specified at 25%.[4] NICE reviewers noted that a 15% margin may be more clinically justified and robust.[4] Stable disease was defined as patients with changes from baseline which were less than or equal to the following criteria : hemoglobin levels decreased by 1.5 g/dL, platelet counts decreased 25%, spleen volume increased 25%, and liver volume increased 20%.[4] In patients treated with eliglustat, 84.8% (95% CI 76.2 to 91.3) of patients maintained disease stability compared to 93.6% (95% CI 82.5 to 98.7) treated with imiglucerase (difference -8.8%; 95% CI -17.6 to 4.2).[4] There were no clinical difference in bone-related outcomes, hemoglobin, platelet count, organ volumes, symptom improvement scores, or health-related quality of life.[4] Eliglustat was compared to placebo in patients who had not had ERT in the previous 9 months (n=40).[4] Compared to placebo at 39 weeks, there were statistically significant differences with eliglustat treatment in all laboratory markers including reduction in spleen volume (MD 30%, 95% CI 36.82 to 23.24; p<0.001), liver volume (MD −6.64%, 95% CI −11.37 to −1.91; p=0.0072), hemoglobin level (MD 1.22 g/dL, 95% CI 0.57 to 1.88; p=0.0006), and platelet count (MD 41.06%, 95% CI 23.95 to 58.17; p<0.0001), but no differences in bone disease or symptom improvement scores at 39 weeks.[4] Data from a small (n=26), single-arm, open-label study provided long-term data for up to 4 years, but data was limited by attrition, small sample size, and risk of reporting bias.[4] Safety analysis included 393 patients. Only 3% of patients discontinued treatment due to adverse events, and most common events occurring in at least 10% of patients included headache, joint pain, nasopharyngitis, upper respiratory tract infections, diarrhea, and dizziness.[4] Applicability of this data is limited as few treatment naïve patients were included in the analysis, few patients were poor CYP2D6 metabolizers, and doses of ERT and eliglustat in clinical trials may not reflect doses typically used in practice.[4] In clinical trials, dose of eliglustat was higher than the FDA-approved labeling in approximately 48% of patients.[4]

After review, 4 systematic reviews were excluded due to poor quality (e.g., network meta-analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). [13-16]

Guidelines:
No high-quality guidelines were identified which met quality inclusion criteria.
After review, 2 guidelines were excluded because they did not meet standard quality criteria.[17,18]

Randomized Controlled Trials:
A total of 86 citations were manually reviewed from the initial literature search. After further review, all trials were excluded because of wrong study design (e.g., observational), comparator (e.g., no control), or outcome studied (e.g., non-clinical).

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Appendix 1: Specific Drug Information

Table A1. Clinical Pharmacology and Pharmacokinetics.

Drug Name/Route	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics
Eliglustat (Cerdelga®), oral[5]	Inhibitor of glucosylceramide synthase which reduces glucosylceramide accumulation in the tissues	Bioavailability 5%	Metabolized via CYP2D6 and CYP3A4; metabolites excreted in urine (42%) and feces (51%)	Varies based on CYP2D6 metabolizer status; lower numbers represent extensive metabolizers and larger numbers represent poor metabolizers • Half-life: 6.5 to 8.9 hr • Cmax: 12 to 137 ng/mL • AUC: 76 to 1057 ng*hr/mL • Vd: 835 L (extensive)
Imiglucerase (Cerezyme®), intravenous[19]	Analogue of human enzyme B-glucocerebrosidase which catalyzes the hydrolysis of glucocerebrosidase to glucose and ceramide and decreases glucocerebrosidase accumulation.	NA	NA	• Half-life: 3-10 minutes • Cmax: NR • AUC: NR • Vd: 0.09 to 0.15 L/kg
Miglustat (Zavesca®), oral[6]	Competitive and reversible inhibitor of glucosylceramide synthase which reduces glycosphingolipid biosynthesis and the amount of glycosphingolipid build-up in tissues	Bioavailability 97% (decreased 36% when administered with food)	Renal excretion; 67% unchanged in urine	• Half-life: 6-7 hours • Cmax: NR • AUC: NR • Vd: 83-105 liters
Taliglucerase alfa (Elelyso®), intravenous[10]	Recombinant analog of human lysosomal glucocerebrosidase that catalyzes the hydrolysis of glucocerebroside to glucose and ceramide and decreases glucocerebrosidase accumulation.	NA	NA	• Half-life: 29-32 hours • Cmax: NR • AUC: 2984 to 6459 ng*h/mL • Vd: 8.8 to 10.7 L
Velaglucerase alfa (Vpriv®), intravenous[11]	Hydrolytic lysosomal glucocerebroside-specific enzyme which catalyzes the hydrolysis of glucocerebroside, reducing the amount of accumulated glucocerebroside.	NA	NA	• Half-life: 11-12 minutes • Cmax: NR • AUC: NR • Vd: 108 mL/kg

Abbreviations: AUC = area under the curve; Cmax = maximum concentration; CYP = cytochrome P450; kg = kilogram; L = liters; NA = not applicable; ng = nanogram; NR = not reported; Vd = volume of distribution

Table A2. Use in Specific Populations

Population	Eliglustat [5]	Imiglucerase[19]	Miglustat [6]	Taliglucerase alfa[10]	Velaglucerase alfa[11]
Pregnancy	Little human data available (20 pregnancies); No effects on pregnancy were noted in rabbit studies, but fetal abnormalities and maternal toxicity were noted in rat studies	No animal reproduction studies conducted	Little human data available. In rat and rabbit studies, decreased live births, maternal death, and decreased fetal weight were observed.	Little human data available. No evidence of embryo-fetal toxicity in rat or rabbit animal studies	Little human data available. No evidence of embryo-fetal toxicity in rat or rabbit animal studies
Lactation	No human data available; drug and metabolites were present in milk in animal studies	No human or animal data available	No data available. Presence in human milk is unknown.	No data available	Presence in human milk is unknown.
Pediatric	Safety and effectiveness in pediatric patients have not been established	Studied in children 2-16 years of age. Safety and efficacy in patients < 2 years has not been established.	Efficacy and safety have not been established	Only 14 pediatric patients were included in clinical trials. Pediatric patients experienced a higher frequency of vomiting (n=4/9) compared to adults. There is insufficient data to inform dosing in patients < 4 years of age.	Studied in children 4-17 years of age (20 pediatric patients). Safety and effectiveness in patients < 4 years of age has not been established.
Geriatric	Studies did not include patients greater than 65 years of age	NA	Studies did not include patients greater than 65 years of age. Caution is recommended due to greater frequency of hepatic, renal and cardiac comorbidities.	There is insufficient data to determine differences between geriatric and adult patients. Only 8 patients greater than 65 years of age were included in clinical trials.	In clinical studies, 56 patients were 65 years of age or older. No differences were observed based on age.
Renal impairment	Avoid use in patient with extensive CYP2D6 metabolism and end stage renal disease or patients with intermediate or poor metabolism and any degree of renal impairment	NA	Dose reduction recommended in patients with renal impairment	NA	NA
Hepatic impairment	Dose adjustment recommended based on degree of impairment, CYP2D6 metabolism, and concomitant use of CYP2D6 or CYP3A4 inhibitors	NA	NA	NA	NA

Drug Safety:
Boxed Warnings: None
Risk Evaluation Mitigation Strategy Programs: None
Contraindications:

- Imiglucerase, miglustat, taliglucerase alfa, velaglucerase alfa: None
- Eliglustat: Patients with altered CYP2D6 metabolism due to risk of cardiac arrhythmias from prolonged PR, QTc, and QRS intervals.[5]
  - Extensive metabolizers who have:
    - moderate or severe hepatic impairment
    - mild hepatic impairment and take a strong or moderate CYP2D6 inhibitor
  - Extensive or intermediate metabolizers who take a strong or moderate CYP2D6 inhibitor and a strong or moderate CYP3A inhibitor
  - Intermediate and poor metabolizers who have:
    - Any hepatic impairment
    - A strong CYP3A inhibitor

Table A3. Summary of Warnings and Precautions.[5,6,10,11,19]

Warning/Precaution	Eliglustat	Imiglucerase	Miglustat	Taliglucerase alfa	Velaglucerase alfa
Hypersensitivity reactions		X (primarily associated with IgG antibodies)		X	X
Development of IgG antibody		X			
Peripheral neuropathy			X		
Tremor			X		
Diarrhea and Weight Loss			X		
Reductions in Platelet Count			X		
ECG changes and potential for cardiac arrhythmias	X				
Pre-existing cardiac conditions	X				
Combination use with Class IA or Class III antiarrhythmic drugs	X				

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) 1946 to April Week 2 2019

1	exp Gaucher Disease/	4473
2	eliglustat.mp.	53
3	imiglucerase.mp.	344
4	miglustat.mp.	382
5	velaglucerase.mp.	72
6	taliglucerase.mp.	32
7	2 or 3 or 4 or 5 or 6	755
8	1 and 7	438
9	limit 8 to (english language and humans)	385
10	limit 9 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	86

Appendix 3: Key Inclusion Criteria

Population	Patients with Gaucher Disease
Intervention	Any FDA-approved pharmacological treatment
Comparator	Placebo or active comparator
Outcomes	Symptoms, morbidity, mortality, quality of life, functional status
Timing	Any duration
Setting	Outpatient

Gaucher Disease

Goal(s):

- Ensure medically appropriate use of drugs for Gaucher disease

Length of Authorization:

Up to 12 months

Requires PA:

- Drugs for Gaucher disease (pharmacy and physician administered claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is the request for continuation of therapy previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the request for treatment of Type 1 Gaucher Disease? Note: Type 1 disease is characterized predominately by bone involvement without CNS symptoms. Efficacy in other types of Gaucher disease has not been established.	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Does the patient have current symptoms characteristic of bone involvement such as: a. Low platelet count with documentation of recent significant bleeding b. Low hemoglobin level and fatigue evaluated using a validated scale (e.g., Brief Fatigue Inventory) c. Radiologic bone disease, T-score less than -2.5 or bone pain d. Delayed growth in children (<10th percentile for age) OR e. Splenomegaly or hepatomegaly associated with abdominal pain or distension?	**Yes:** Go to #6 Document baseline labs and symptoms	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the request for combination treatment with more than one targeted therapy for Gaucher disease?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #7
7. Is the request for enzyme replacement therapy?	**Yes:** Go to #8	**No:** Go to #9
8. Will the prescriber consider a change to a preferred product? Message: Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class. Approve preferred therapy for up to 6 months.	**No:** Approve for up to 6 months
9. Does the patient have a documented contraindication, intolerance, or inadequate response to enzyme replacement therapy?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
10. Is the request for eliglustat?	**Yes:** Go to #11	**No:** Approve for up to 6 months

Approval Criteria		
11. Does the patient have cardiac disease or long-QT syndrome or is currently taking a Class IA or Class III antiarrhythmic medication?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #12
12. Does the patient have moderate to severe hepatic impairment?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #13
13. Does testing for CYP2D6 metabolizer status indicate extensive, intermediate or poor CYP2D6 metabolism?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; medical appropriateness
14. Is the dose consistent with FDA labeling based on CYP2D6 metabolism and use of concomitant CYP inhibitors (see FDA labeling for full details)?	**Yes:** Approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there documentation based on chart notes that the patient experienced a significant adverse reaction related to treatment for Gaucher disease?	**Yes**: Go to #2	**No:** Go to #3
2. Has the adverse event been reported to the FDA Adverse Event Reporting System?	**Yes:** Go to #3 Document provider attestation	**No:** Pass to RPh. Deny; medical appropriateness
3. Is there objective documentation of benefit based on improved labs or patient symptoms?	**Yes:** Approve for up to 12 months Document labs and patient symptoms	**No:** Pass to RPh. Deny; medical appropriateness