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Drug Class Literature Scan: Fabry Disease

Date of Review: April 2022

Date of Last Review: September 2019
Literature Search: 01/01/2019 – 01/14/2022

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:
- No new high-quality systematic reviews or guidelines were published since the last Fabry Disease class update.
- Fabrazyme (agalsidase beta) received expanded FDA approval in March 2021 for use in patients aged 2 years and older with confirmed Fabry disease.[1] Prior to the expanded indication approval, the manufacturer's label stated the safety and effectiveness of agalsidase beta had not been established in pediatric patients less than 8 years of age.[2]

Recommendations:
- Revise prior authorization (PA) criteria to reflect expanded indication for agalsidase beta.

Summary of Prior Reviews and Current Policy
- Therapeutic agents to manage the lysosomal storage disorder Fabry disease were reviewed by the Pharmacy and Therapeutics (P & T) Committee in September 2019. Fabry disease is a funded condition on line 60 (metabolic disorders) of the Health Evidence Review Commission (HERC) prioritized list of health services.[3] After review, the committee designated agalsidase beta and migalastat as non-preferred agents on the Preferred Drug List (PDL) of the Oregon Practitioner-Managed Prescription Drug Plan (PMPDP) and approved PA criteria for the Fabry disease treatments to ensure use according to FDA-approved indications (**Appendix 4**). At the time of 2019 review, there was insufficient evidence for the effectiveness of agalsidase in delaying the onset, or reducing the incidence and severity, of Fabry disease-related complications, and its impact on long-term survival remained unclear. Published data were not yet available on the effects of migalastat in patients with more advanced Fabry disease and with duration of therapy beyond 2 years.[4] There was insufficient data regarding the long term clinical outcomes of migalastat therapy or comparison with agalsidase beta.
- Since 2020, 60 patients under the Oregon Health Plan had claims associated with Fabry disease. Of these 60 patients, 3 were enrolled in Fee-For-Service (FFS), 53 were enrolled in a Coordinated Care Organization (CCO), and 4 patients were no longer eligible. There have been no pharmacy claims for migalastat in the past 12 months in FFS or CCO populations. In 2021, there were 13 patients in the CCO population with physician administered claims for agalsidase beta.

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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 literature scan is available in **Appendix 3**, 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.

New Systematic Reviews:
After review, 1 systematic reviews was excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[5]

New Guidelines:
High Quality Guidelines: No new guidelines have been published or updated since the last Fabry Disease class update in 2019.

Additional Guidelines for Clinical Context:
In 2020, the National Society of Genetic Counselors (NGSC) published a focused revision for the 2013 Fabry Disease Practice Guidelines.[6] New information related to newborn screening, disease incidence, and treatment were provided to reflect current knowledge of Fabry Disease.[6] Guidance for free Fabry Disease diagnostic screening was added to the report. Migalastat indications, dosing and associated adverse effects were described. Finally, a summary of adverse outcomes associated with Fabry Disease and strong guidance to initiate enzyme replacement therapy in childhood to reduce disease impact were discussed.[6]

After review, 0 guidelines were excluded due to poor quality.

New Indications:
Fabrazyme (agalsidase beta) received expanded FDA approval March 2021 for use in patients aged 2 years and older with confirmed Fabry disease.[1] Prior to the expanded indication approval, the manufacturer's label stated the safety and effectiveness of agalsidase beta had not been established in pediatric patients less than 8 years of age.[2] The safety and effectiveness of Fabrazyme have been established in pediatric patients based on adequate and well-controlled studies in adults and a single-arm, open-label study in 16 pediatric patients (14 males, 2 females) with Fabry disease aged 8 to 16 years.[1] Additional data in 24 patients with Fabry disease aged (mean age 12 years) provided support for use in pediatric patients.[7]

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Agalsidase beta	FABRAZYME	03/11/2021	Warnings and Precautions	In clinical trials and post marketing safety experience with FABRAZYME, approximately 1% of patients developed anaphylactic or severe hypersensitivity reactions during FABRAZYME infusion. Four serious infusion-associated reactions occurred in 3 patients during FABRAZYME infusions, including bronchospasm, urticaria, hypotension, and development of FABRAZYME-specific antibodies. Other infusion-associated reactions occurring in more than one patient during the study included rigors, hypertension, nausea, vomiting, and pruritus.[1] Higher incidences of hypersensitivity reactions were observed in adult patients with persistent anti-FABRAZYME antibodies and in adult patients with high antibody titer compared to that in antibody negative adult patients.[1] Physicians should consider testing for IgE antibodies in patients who experienced suspected hypersensitivity reactions and consider the risks and benefits of continued treatment in patients with anti-FABRAZYME IgE antibodies. There are no marketed tests for antibodies against FABRAZYME. If testing is warranted, contact Genzyme Corporation at 1-800-745-4447.[1] Patients who have had a positive skin test to FABRAZYME or who have tested positive for FABRAZYME-specific IgE antibody have been rechallenged with FABRAZYME using a rechallenge protocol. Rechallenge of these patients should only occur under the direct supervision of qualified personnel, with appropriate medical support measures readily available.[1] Infusion-associated reactions are defined as adverse reactions occurring on the same day as the infusion. The incidence of infusion- associated reactions was higher in patients who were positive for anti-FABRAZYME antibodies than in patients who were negative for anti-FABRAZYME antibodies.[1]
Migalastat	GALAFOLD	9/25/2020	Use in Specific Populations	<u>Pregnancy Exposure Study</u> There were 3 pregnant women with Fabry disease exposed to GALAFOLD in clinical trials. As such, the available data are not sufficient to assess drug associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, no adverse developmental effects were observed.[8]

				Lactation There is a study that collects data on effects of GALAFOLD on lactation for women with Fabry disease and their neonates and infants up to 1 year of age who are exposed through breast milk. Healthcare providers are encouraged to register patients or obtain additional information by contacting the Pregnancy Coordinating Center at 1-888-239-0758, email fabrypregnancy@ubc.com, or visit www.fabrypregnancyregistry.com.[8]

References:

1. FABRAZYME (agalsidase beta) for injection. Prescribing Information. Cambridge, MA; Genzyme Corporation. March 2021.
2. FABRAZYME (agalsidase beta) IV Injection Prescribing Information. Genzyme Corporation; Cambridge, MA. December 2018.
3. Oregon Health Authority, Oregon Health Evidence Review Commission. Prioritized List of Health Services. 1/1/2019. https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Prioritized-List.aspx. Accessed August 5, 2019.
4. Center for Drug Evaluation and Research. Galafold Review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/208623Orig1s000MultidisciplineR.pdf Accessed July 24, 2019.
5. Sheng S, Wu L, Nalleballe K, et al. Fabry's disease and stroke: Effectiveness of enzyme replacement therapy (ERT) in stroke prevention, a review with meta-analysis. *Journal of Clinical Neuroscience.* 2019;65:83-86.
6. Henderson N, Berry L, Laney DA. Fabry Disease practice resource: Focused revision. *J Genet Couns.* 2020;29(5):715-717.
7. Ries M, Clarke JT, Whybra C, et al. Enzyme-replacement therapy with agalsidase alfa in children with Fabry disease. *Pediatrics.* 2006;118(3):924-932.
8. GALAFOLD (migalastat) oral capsules. Prescribing Information. Cranbury, NJ; Amicus Therapeutics, Inc. 12/21.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
agalsidase beta	FABRAZYME	VIAL	N
migalastat	GALAFOLD	CAPSULE	N

Appendix 2: New Comparative Clinical Trials

A total of 16 citations were manually reviewed from the initial literature search. After further review, 16 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to January Week 1 2022, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 14, 2022

1.	Fabry Disease/	3037
2.	alpha-Galactosidase/	2297
3.	Migalastat.mp.	138
4.	2 or 3	2355
5.	1 and 4	1494
6.	limit 5 to (english language and humans)	1301
7.	limit 6 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	16

Fabry Disease

Goal(s):

- Ensure medically appropriate use of drugs for Fabry Disease

Length of Authorization:

- Up to 12 months

Requires PA:

Agalsidase beta (pharmacy and physician administered claims) and migalastat

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 this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is this a request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to # 5
5. Is the provider a specialist in managing Fabry disease?	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the request for migalastat?	**Yes:** Go to # 7	**No:** Go to # 10
7. Does the patient have a mutation that is amenable to migalastat therapy as confirmed by a genetic specialist?	**Yes**: Got to # 8	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
8. Is the patient currently receiving agalsidase beta?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to # 9
9. Is the patient 18 years of age or older?	**Yes**: Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness. Migalastat is only FDA-approved for use in adults.
10. Is the patient a male at least 2 years of age with diagnosis of Fabry disease confirmed by genetic testing or deficiency in alpha-galactosidase A enzyme activity in plasma or leukocytes?	**Yes:** Go to # 11	**No:** Go to # 12
11. Does the patient have end stage renal disease requiring dialysis?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 12 months
12. Is the patient a female at least 2 years of age and a documented Fabry disease carrier confirmed by genetic testing with significant clinical manifestations of Fabry disease such as: • Uncontrolled pain that interferes with quality of life • Gastrointestinal symptoms that are significantly reducing quality of life and not attributable to other pathology • Mild to moderate renal impairment (GFR > 30 mL/min) • Cardiac disease (left ventricular hypertrophy, conduction abnormalities, ejection fraction< 50%, arrhythmias) • Previous stroke or TIA with retained neurologic function	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient's condition improved as assessed by the prescribing provider and provider attests to patient's improvement in one of the following: • Renal function • Pain Scores • Quality of Life measurement • Cardiac function • Neurologic status • Growth and development in children	**Yes:** Approve for 12 months. Document baseline assessment and provider attestation received.	**No**: Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 4/22 (DM); 9/19 (DM)
Implementation: 5/1/22; 11/1/19