

August 25, 2019

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Dear Drs. Citron and Moretz:

Thank you for the opportunity to review and provide comments as requested on “Drug Class Review and New Drug Evaluation: Targeted Therapies for Fabry Disease.” Our goal is to facilitate consideration of more recent clinical data including recent systematic reviews and consensus guidelines by bringing them to your attention in your efforts to create a set of guidelines advancing and enriching the quality of patient care in Oregon.

Towards this aim we have highlighted a number of conclusions, results, and items from recent systematic reviews, selected clinical studies, and consensus guidelines which may not have been included in the draft, “Drug Class Review and New Drug Evaluation: Targeted Therapies for Fabry Disease,” reviewed by us. These highlighted items are neither meant to be comprehensive or exhaustive in themselves; we would ask you to refer to the original publications instead. (Note: [refs] = please refer to the original citations and references in the published paper).

### **I. Challenges of Analyzing Clinical Evidence in Rare Disease**

The analysis of published literature in patients with Fabry disease and other rare diseases is challenging given the need to acknowledge both the clinical and genetic heterogeneity of the patient population, as well as, the limited clinical evidence available for various outcomes given the low prevalence of disease in the overall population.

Tingley K et al. (2018) note the following in evaluating efficacy in any rare disease:

(1) “For many rare diseases, strong analytic study designs for evaluating the efficacy and effectiveness of interventions are challenging to implement because of small, geographically dispersed patient populations and underlying clinical heterogeneity. The objective of this study was to integrate perspectives from published literature and key rare disease stakeholders to better understand the perceived challenges and proposed methodological approaches to research on clinical interventions for rare diseases.” [p. 1]

(2) “There was agreement across the focus group interviews and with the literature we reviewed that the main challenges in generating robust treatment efficacy and effectiveness evidence for rare diseases includes: i) limitations in recruiting a sufficient sample size to achieve planned statistical power for many rare diseases [...]; ii) difficulties in accounting for characteristic clinical heterogeneity of many rare diseases; and iii) frequent reliance on short-term, surrogate outcomes whose clinical relevance is often unclear..” [p. 15]

Elliott PM et al. (2019) note the following:

(1) “Fabry disease is a rare disease. With such small patient numbers, it is challenging to design sufficiently powered randomised, placebo-controlled clinical trials. Consequently, publications derived from disease registries and case studies are common. However, Fabry disease is also very heterogeneous, with different clinical manifestations in patients with GLA variants associated with classic versus late-onset disease, in males versus females, and even within females depending on their level of X-chromosome inactivation (Ref).” [Introduction, p. 1]

(2) “We have demonstrated the value of performing an unpooled systematic literature review of all published evidence of ERT outcomes in Fabry disease, highlighting that in a rare genetic disorder like Fabry disease, which is phenotypically diverse, different patient populations can require different disease management and therapeutic goals depending on age, genotype, and disease severity/level of organ involvement.” [Abstract, p. 1]

## **II. Systematic Reviews Addressing ERT Efficacy in Fabry Disease**

### **ERT Efficacy in Adult Male Patients with Fabry Disease**

Germain DP et al. (2019) performed a comprehensive systematic literature review of all original articles on ERT in the treatment of Fabry disease published through January 2017 focusing on the efficacy of ERT in adult male patients.

(Germain DP et al. The effect of enzyme replacement therapy on clinical outcomes in male patients with Fabry disease: A systematic literature review by a European panel of experts. Mol Genet Metab Rep. 2019 Feb 6;19:100454. doi: 10.1016/j.ymgmr.2019.100454. PMID: 30775256.)

#### **Results:**

“Clinical evidence for the efficacy of ERT in adult male patients was available from 166 publications including 36 clinical trial publications. ERT significantly decreases globotriaosylceramide levels in plasma, urine, and in different kidney, heart, and skin cell types, slows the decline in estimated glomerular filtration rate, and reduces/stabilizes left ventricular mass and cardiac wall thickness. ERT also improves nervous system, gastrointestinal, pain, and quality of life outcomes.” [Abstract, pp. 1-2]

#### **(1) Regarding ERT efficacy:**

“ERT was the first disease-specific therapy available that changed the natural history of Fabry disease. Data published in adult male patients with Fabry disease demonstrates that the effect of ERT on plasma GL-3 levels, eGFR, and cardiac outcomes is strongest and substantiated by a wide range of publications, showing consistent, dose-dependent reductions in GL-3 accumulation, a reduced decline in eGFR, and improvements in cardiac outcomes...” [Discussion, p. 14]

#### **(2) Regarding early ERT initiation for cardiac disease:**

“Patients who started ERT at an earlier age achieved better outcomes [...] effective early treatment is needed to prevent or mitigate disease progression [...]. Regarding cardiac function, patients who started agalsidase beta treatment at age <30 years experienced a statistically significant decline in LVM but those who started ERT at age ≥50 years reported an increase in LVM” [Discussion, p. 15]

### (3) Regarding early ERT initiation for renal disease:

“[...] initiation of treatment before the development of significant glomerulosclerosis and proteinuria might prevent future renal disease [...], which correlates with the reduced slope of eGFR decline that is seen in patients who started ERT early compared with a higher slope of eGFR decline in patients who started ERT later”. [Discussion, p. 15]

### Conclusions:

“ERT is a disease-specific treatment for patients with Fabry disease [...]. Better outcomes may be observed when treatment is started at an early age prior to the development of organ damage such as chronic kidney disease or cardiac fibrosis. Consolidated evidence suggests a dose effect.” [Abstract, p. 2]

### **ERT Efficacy in Adult Female Patients with Fabry disease**

Germain DP et al. (2019) performed a comprehensive systematic literature review of all original articles on ERT in the treatment of Fabry disease published through January 2017 focusing on the efficacy of ERT in adult female patients.

(Germain DP et al. The effect of enzyme replacement therapy on clinical outcomes in female patients with Fabry disease - A systematic literature review by a European panel of experts. Mol Genet Metab. 2019 Mar;126(3):224-235. doi: 10.1016/j.ymgme.2018.09.007. PMID: 30413388.)

### Results:

"Clinical evidence for the efficacy of ERT in female patients was available from 67 publications including six clinical trial publications, and indicates significant reductions in plasma and urine globotriaosylceramide (GL-3) accumulation (in female patients with elevated pre-treatment levels) and improvements in cardiac parameters and quality of life (QoL)." [Abstract, p. 1]

### (1) Regarding ERT efficacy in cardiac disease:

“LVMi outcomes were reported in one OS publication in a cohort of 22 female patients with a mean age of 44 years who were treated with agalsidase beta for a median of 36 months. 12 patients had LVH at baseline. Treatment resulted in a significant reduction in LVMi from baseline, as assessed using echocardiography [Motwani M et al. 2012].” [Cardiac outcomes, p. 230, see Selected Study]

### (2) Regarding ERT efficacy in renal disease:

Evidence suggests that ERT stabilizes kidney function.

(a) Renal function/GFR: “Publications of data from mixed-ERT studies also show that ERT is associated with stable eGFR in female patients, reporting no or minimal declines in eGFR in line with normal age-related changes in renal function [...]” [Results, p. 229]

(b) Proteinuria: “Publications reporting proteinuria outcomes from mixed-ERT OS in 17 female patients (age at ERT 33–79 years) described an improvement in albuminuria during ERT treatment (duration 6–26 months) [...], a non-significant inverse association between time on ERT and the likelihood of developing proteinuria (analysis in 158 females) [...], and significant improvements in proteinuria during treatment (13 patients, mean age 45 years, 6-years follow-up)...” [Results, p. 229]

### Conclusions:

“This review of available literature data demonstrates that ERT in adult female patients with Fabry

disease has a beneficial effect on GL-3 levels and cardiac outcomes. The current evidence also suggests that ERT may improve QoL in this patient population.” [Abstract, p. 224]

## **ERT Efficacy in Children and Pediatric Patients with Fabry disease**

Spada et al. (2019) performed a comprehensive systematic literature review of all original articles on ERT in the treatment of Fabry disease published through January 2017 focusing on the efficacy of ERT in children and pediatric patients including a total of 34 publications which reported ERT outcomes data in pediatric patients.

“A comprehensive systematic review of published literature on ERT in Fabry disease was conducted in January 2017. The literature analysis included all original articles reporting outcomes of ERT in paediatric patients [...] (patients  $\leq$  18 years of age) published up to 31 January 2017.” [Abstract, p. 1]

### **Results:**

“Treatment-related outcomes in the paediatric population were reported in six publications derived from open-label clinical trials and in 10 publications derived from observational or registry-based studies. ERT was shown to significantly reduce plasma and urine GL-3 levels in paediatric patients with Fabry disease. The effect of ERT on GL-3 clearance from renal podocytes appeared to be agalsidase dose-dependent. ERT relieved pain and improved gastrointestinal symptoms and quality of life.” [Abstract, p. 1]

#### **(1) Regarding ERT efficacy overall:**

“ERT significantly reduced or normalized plasma GL-3 levels, relieved pain, improved gastrointestinal symptoms, and increased quality of life [Refs]. Some patients were able to reduce or discontinue the use of pain medication [Refs]. The management of pain is particularly important in children [Refs] as pain relief – or decrease in use of symptomatic neuropathic pain-control medications – can reduce sedation, improve concentration, and lessen school absences....” [Discussion, p. 10]

#### **(2) Regarding ERT efficacy in renal disease:**

Evaluating effect of agalsidase beta on proteinuria: “One single-arm CT publication including 16 paediatric patients (14 males) reported a slight reduction in mean urinary protein excretion after 11 months of treatment with agalsidase beta [Wraith JE et al., 2008]. Mild proteinuria ( $>100$  mg/m<sup>2</sup>/24 h) was present in 8 of 15 evaluable patients before treatment, but in only three patients at the end of follow-up [Wraith JE et al. 2008].” Overall, the authors concluded: “ERT has been shown to normalize plasma GL-3 levels and to clear GL-3 inclusions from renal cells, with a dose-dependent mechanism in podocytes.” [Results, p. 8, see Selected Study]

#### **(3) Regarding ERT efficacy in reducing GI outcomes:**

“A single-arm CT of 16 paediatric patients treated with agalsidase beta reported a significant improvement in postprandial pain and vomiting, and a non-significant decline in nausea [Wraith JE et al. 2008]. In another OS publication, VAS scores for abdominal pain were reduced in both male and female patients following 12–96 months of treatment [Borgwardt L et al. 2013]” [Results, p. 10]

#### **(4) Regarding ERT efficacy in improving quality of life:**

“...study of agalsidase beta, 48 months of treatment in 16 paediatric patients (14 males) was associated with improvement in a range of QoL parameters including significantly reduced proportion of days absent from school due to illness, increased proportion of days where patients could report good

general health, and a decrease in the number of days when the patients experienced difficulty in performing low, medium, and high-energy activities [Wraith JE et al. 2008]. An increase in energy levels and the ability to perform physical exercise in 10 paediatric patients (six males) was also reported in another OS publication...[Borgwardt L et al. 2013].”

#### Conclusions:

”ERT has a beneficial clinical impact in paediatric patients with Fabry disease, as it can relieve neuropathic pain, ameliorate gastrointestinal symptoms and improve quality of life. Moreover, ERT has been shown to normalize plasma GL-3 levels and to clear GL-3 inclusions from renal cells, with a dose-dependent mechanism in podocytes.” [Discussion, p. 10]

### **III. Selected Clinical Studies**

As noted by Wanner C et al. (2018) (see below) in the set of recent organ-specific therapeutic goals for Fabry disease developed by a European panel, it is important to recognize that a primary positive result regarding treatment efficacy in chronic disease (by comparison to acute/subacute disease) is the stabilization of, or maintenance without change in, clinical marker(s) tied to end-organ function.

#### **Fabry Renal Disease Natural History**

##### Proteinuria

A. Schiffman R et al. (2009) provided evidence for the relationship between increasing proteinuria and renal function decline in ERT-naïve Fabry patients. This association is consistent with those established in other proteinuric chronic kidney diseases.

##### Findings:

In 447 ERT-naïve Fabry patients (n=279 M, 168 F; 27 sites) followed for a median of 12 years:

- (1) In patients with eGFR  $\geq 60$  ml/min/1.73 m<sup>2</sup>, the onset of renal function decline occurred at age 20 in males (-3.0 ml/min/1.73 m<sup>2</sup>/yr) and at 30 years in females (-0.9 ml/min/1.73 m<sup>2</sup>/yr)
- (2) Increasing proteinuria (<0.1,  $\geq 0.1$  to <1.0,  $\geq 1.0$  g/24hr) was associated with greater rates of renal function decline both in males (-1.6, -3.3, -6.9 ml/min/1.73 m<sup>2</sup>/yr) and females (-0.6, -2.2, -4.6 ml/min/1.73 m<sup>2</sup>/yr) over 1 year
- (3) The mean age of death in ERT-naïve males (n=20) was 49.9 years

B. Wanner C. et al. (2010) evaluated the relationship between renal function decline and severity of proteinuria in 462 untreated patients (121 M, 341 F) from the Fabry Registry.

##### Findings:

- (1) Men overall (71%) experienced more rapid renal function decline than the normal adult population (loss of eGFR  $> -1$  ml/min per 1.73 m<sup>2</sup> per year), whereas a smaller fraction of women (39%) experienced rapid renal function decline
- (2) Patients experiencing rapid renal function decline had significantly higher mean averaged urinary protein to urinary creatinine ratios (UP/Cr) than patients exhibiting slower progression (1.5 versus 0.2 for men; 1.4 versus 0.5 for women; P < 0.0001).

##### Conclusions:

Regression models of eGFR slope indicated that UP/Cr is the most important indicator of renal disease progression in adult Fabry patients.

## ERT Clinical Efficacy in Disease Progression

### ERT Efficacy in Renal Disease Progression

A. Tøndel C et al. evaluated renal biopsies in 12 consecutive patients (11 M, 1 F; ages 7 to 33; pre-treatment mean eGFR=105.8 ml/min/1.73 m<sup>2</sup>; post-treatment mean eGFR=107.3 ml/min/1.73 m<sup>2</sup>) at baseline and at 5 years, before and after 5 years of ERT (agalsidase alfa or agalsidase beta, median 65 months); 7 patients had additional biopsies at 1 and 3 years.

#### Findings:

- (1) At 65 months, all patients showed clearance of glomerular endothelial and mesangial cell GL3 inclusions; 4 patients who received the highest dose of agalsidase exhibited significant clearance of podocyte cell inclusions compared to patients who received the lowest dose (p=0.011).
- (2) Microalbuminuria resolved in 5 patients (age ≤17); baseline microalbuminuria remained stable in 4 patients (age ≥18); baseline normoalbuminuria remained stable in 2 patients; albuminuria increased in 1 patient (age 17).
- (3) Regression analysis showed a correlation between podocyte GL3 inclusion clearance and decrease in albumin/Cr ratio (r=0.837, p=0.007)
- (4) Regression analysis showed a correlation between podocyte GL3 clearance and cumulative agalsidase dose (r=0.804, p=0.002).

B. Germain DP et al. (2015) observed that patients started on agalsidase beta at a later age with greater renal disease (increased proteinuria, percentage of sclerotic glomeruli by renal biopsy) exhibited a more rapid decline in renal function compared to younger patients initiated on treatment with less severe renal disease thus underscoring the importance of early initiation of agalsidase. Phase 3 Clinical Trial patients enrolled in the Fabry Registry who continued agalsidase beta (n=50 M; 2 F) were stratified by renal involvement at 10-year followup: LRI group (low renal involvement: Urine protein/Cr ≤0.5 g/g and <50% sclerotic glomeruli), mean age 25.3, baseline eGFR=126.0 ml/min/1.73 m<sup>2</sup>, Urine protein/Cr=0.2 were compared to a HRI group (high renal involvement: Urine protein/Cr >0.5 g/g or ≥50% sclerotic glomeruli) mean age 37.7, baseline eGFR=101.6 ml/min/1.73 m<sup>2</sup>, Urine protein/Cr=1.3.

#### Findings:

- (1) LRI patients starting agalsidase beta at a younger age than HRI patients (difference=12.4 yrs) exhibited a smaller mean renal decline=-1.89 mg/ml/1.73 m<sup>2</sup> compared to HRI patients with a renal function decline=-6.82 mg/ml/1.73 m<sup>2</sup>.
- (2) 81% (42/52) of combined agalsidase-treated patients remained free of severe clinical events over 10 years.

### ERT Efficacy in Cardiac Disease Progression

A. Motwani M et al. (2012) evaluated cardiac function (left ventricular mass index, LVMI; maximal wall thickness, MWT; left ventricular end-diastolic diameter, LVEDD; ejection fraction, EF) at baseline and after long-term agalsidase beta therapy (median 36 months) in 66 local U.K. registry patients.

#### Findings:

- (1) "The overall mean LVMI and MWT were significantly reduced by ERT at follow-up (LVMI: 116 ± 28 vs. 113 ± 26 g/m<sup>2</sup>, MWT: 14 ± 6 vs. 13 ± 5 mm; both p values < 0.001) (Table 2, Fig. 1). On sub-group analysis this improvement was seen in both sexes; and in both mild and moderate/severe disease

groups (all p values < 0.05)” [Results, p. 199]

(2) “On LVH status sub-group analysis, 42 patients (64%) were found to have LVH at baseline [...] In these patients, mean LVMI, MWT and LVEDD were significantly reduced by ERT (LVMI:  $135 \pm 13$  vs.  $133 \pm 13$  g/m<sup>2</sup>, MWT:  $17 \pm 6$  vs.  $16 \pm 5$  mm, LVEDD:  $55 \pm 6$  vs.  $54 \pm 6$  mm; all p values < 0.05).” [Results, p. 199]

## ERT Efficacy in Multi-Organ Disease Progression

A. Effect of agalsidase on multi-organ disease progression was examined by Banikazemi et al. (2007) in a double-blind, placebo-controlled trial in 82 classic Fabry patients (n=72 M, 10 F) with baseline chronic kidney disease (mean baseline SCr 1.6 mg/dL) to evaluate the effect of agalsidase beta on disease progression (mean treatment duration=18.4 months) using a composite outcome (renal, cerebrovascular, cardiac, death): Treatment group, n=51 (mean age=46.9, eGFR=53 mg/ml/1.73 m<sup>2</sup>) vs. placebo group, n=31 (mean age=44.3, eGFR=52 mg/ml/1.73 m<sup>2</sup>).

### Findings:

(1) Intention-to-treat analysis of time-to-first clinical event adjusted for baseline proteinuria showed that agalsidase was associated with a lower risk (HR=0.47, 0.21-1.0, p=0.06) of the composite endpoint (renal, cerebrovascular, cardiac, death) than placebo (p=0.06).

(2) Subgroup analysis of protocol-adherent patients showed a significant reduction of risk (HR=0.39, 0.16-0.93, p=0.034).

### Conclusions:

(1) "Agalsidase-beta therapy slowed progression to the composite clinical outcome of renal, cardiac, and cerebrovascular complications and death compared with placebo in patients with advanced Fabry disease. Therapeutic intervention before irreversible organ damage may provide greater clinical benefit." [Abstract, p. 77]

(2) "This randomized, double-blind, placebo-controlled trial showed that agalsidase-beta therapy reduced the likelihood of any clinical event (composite outcome) in patients with advanced Fabry disease, indicating a slower progression of severe manifestations." [Discussion, p. 83]

## IV. General Consensus Guidelines

A European panel of experts collaborated to develop a set of organ-specific therapeutic goals for Fabry disease (Wanner C et al. (2018)).

“For each organ system, optimal treatment strategies accounted for inter-patient differences in disease severity, natural history, and treatment responses [...] consensus therapeutic goals and proposed patient management algorithm take into account the need for early disease-specific therapy to delay or slow the progression of disease...” [Abstract, pp. 189-190]

“The systematic literature review and the meetings of the European expert panel were sponsored by Sanofi Genzyme. This paper presents the consensus reached on therapeutic goals drafted by specialist working groups, tasked with developing therapeutic goals for the heart, kidney, and nervous system in addition to an overall consensus on the goals for treatment of other organ manifestations of Fabry disease.” [Methods, p. 190]

### (1) Regarding ERT in cardiac outcomes:

(a) “Cardiac manifestations are common in Fabry disease, occurring in 40–60% of patients [...] spectrum

of cardiac complications is similar in both the classic and the later-onset cardiac phenotype...Cardiac complications are the leading cause of death in male and female patients with Fabry disease [Waldek S et al. 2009]. [...] Cardiomyopathy in Fabry disease is characterised by LVH and an increase in left ventricular mass (LVM)." [Heart Involvement, p. 192]

(b) Clinical and observational evidence suggests that cases of mild and moderate LVH can be improved with ERT, whereas patients with severe LVH can be stabilized [...]. Clinical experience indicates that sustained treatment is required to determine the response of LVH to ERT...." [Heart Involvement, p. 192]

(2) Regarding ERT in renal outcomes:

(a) "...kidney pathology is associated with progressive CKD with increasing albuminuria leading to overt proteinuria and reduced GFR, ultimately progressing to end-stage kidney disease (ESKD), if untreated [Refs]" [Kidney Involvement, p. 193]

(b) "Effective management of underlying kidney pathology hinges upon early diagnosis and timely initiation of ERT at a young age [Tøndel C et al. 2013]. Registry and clinical trial data have shown that patients who initiate ERT at a younger age, soon after the onset of symptoms, benefit the most from ERT and have more favourable long-term renal outcomes [Refs] [...] because significant glomerular and vascular damage can develop prior to the emergence of albuminuria or changes in GFR, and seems reversible only at an early stage [Refs]." [Kidney Involvement, p. 193]

(c) Stabilization of function is achieved if a patient has a GFR slope loss  $\leq 1-3$  mL/min/1.73m<sup>2</sup>/year...." [Kidney Involvement, p. 194]

(d) "In Fabry nephropathy, there is a relationship between CKD stage and degree of proteinuria; higher degrees of proteinuria are usually seen in patients with more advanced CKD, and higher baseline proteinuria levels have also been shown to be a significant indicator of faster GFR decline [refs]. This requires the use of adjunctive therapies (e.g. ACEi or ARB) in addition to ERT, as ERT alone does not appear to have significant effects on proteinuria, though there is evidence that ERT can reduce (micro)albuminuria [Germaine DP et al. 2015; Wanner C et al. 2010]." [Kidney Involvement, p. 194, see Selected Study]

(e) Additionally, it is important to initiate ERT early in the disease course as substantial, irreversible organ damage can occur prior to overt proteinuria [refs]. For paediatric and adult patients with normal urinary albumin excretion levels when initiating ERT, the therapeutic goal should be to avoid the development of albuminuria..." [Kidney Involvement, p. 194]

#### Conclusions:

"The overall therapeutic goals for Fabry nephropathy, depending on the individual patient's clinical condition, are to prevent the development of albuminuria, stabilize albuminuria or prevent, avoid, or delay progression to overt proteinuria, and stabilize kidney function." [Kidney Involvement, p. 194]

## V. Consensus Guidelines Regarding Initiation and Indication for ERT

### **Recommendations for Fabrazyme in the treatment of patients with Fabry disease**

Fabrazyme is indicated for use in patients with Fabry disease. Fabrazyme reduces globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and certain other cell types (USPI, Dec. 2018).

In addition to the consensus guidelines published by Wanner C et al. (2018), two other recent consensus guidelines (below) have been published, one for adults and one for children, which include guidelines regarding the initiation of ERT.

Ortiz A et al. Fabry disease revisited: Management and treatment recommendations for adult patients. *Mol Genet Metab.* 2018 Apr;123(4):416-427. doi: 10.1016/j.ymgme.2018.02.014. PMID: 29530533.

Methods:

"The development of these recommendations was initiated in July 2014 at a meeting of an international panel of Fabry disease experts from seven subspecialties, including nephrology, cardiology, neurology, genetics, genetic counseling, pediatrics, and metabolic disorders convened in Atlanta, GA, USA, to review existing treatment guidelines for adults with Fabry disease [17]. Subsequent discussions were held during a panel meeting in February 2015 in Orlando, FL, USA." [Introduction, p. 417]

This guideline makes the following statements and recommendations:

(1) "It has become increasingly clear that comprehensive and timely treatment of adult patients with Fabry disease should be directed to-ward prevention of (further) progression to irreversible tissue damage and organ failure." [Clinical Management of Adult Patients with Fabry Disease, p. 419]

(2) Male patients (symptomatic or asymptomatic): "ERT should be considered and is appropriate in all patients at any age of presentation" [Initiation of Enzyme Replacement Therapy, p. 421, Table 2]

(3) "ERT with agalsidase is a cornerstone of therapy, and there is growing evidence that the clinical response to treatment is improved with early ERT initiation. Ideally, adult male patients with a classic Fabry mutation should initiate ERT promptly, regardless of Fabry symptoms, with appropriate adjunctive treatment for symptomatic management." [p. 424]

(4a) Female patients, symptomatic: "Signs/symptoms suggesting major organ involvement, warranting initiation of ERT" [p. 421, Table 2]

(4b) Female patients, asymptomatic: "ERT should be considered if there is laboratory, histological, or imaging evidence of injury to the kidney, heart, or the CNS" and "ERT should also be considered if a skewed X chromosome inactivation pattern with predominant expression of the mutant GLA allele with or without very low  $\alpha$ -Gal A activity have been demonstrated in the presence of signs and symptoms of disease [p. 421, Table 2]

(5) With respect to male and female patients with late-onset (non-classic) Fabry disease often associated with solitary end-organ involvement: "ERT should be considered and is appropriate if there is laboratory, histological, or imaging evidence of injury to the kidney, heart, or the CNS, as detailed above, even in the absence of typical Fabry symptoms. The abnormalities should be attributable to Fabry disease; this may require histological assessment or biochemical evidence of GL-3 accumulation" [p. 421, Table 2]

**Recommendations for Fabrazyme in the treatment of children with Fabry disease**

A. Hopkin RJ et al. The management and treatment of children with Fabry disease: A United States-based perspective. Mol Genet Metab. 2016 Feb;117(2):104-13. doi: 10.1016/j.ymgme.2015.10.007. PMID: 26546059.

(1) " Recommendations for ERT initiation are provided in Table 3. Patients reporting Fabry-related symptoms should consider treatment, regardless of age or sex. This includes patients with mild symptoms, as any symptoms reflect underlying disease progression. [Recommendations for ERT Initiation, p. 110]

(2) "Treatment with ERT should be considered and is appropriate if Fabry symptoms are present in boys or girls at any age." [Recommendations for ERT Initiation, p. 110, Table 3]

B. Ortiz A et al. Fabry disease revisited: Management and treatment recommendations for adult patients. Mol Genet Metab. 2018 Apr;123(4):416-427. doi: 10.1016/j.ymgme.2018.02.014. PMID: 29530533.

(1) "One vital area of focus, however, is the timing for ERT initiation. The importance of early initiation of ERT has been highlighted in treatment guidelines for pediatric patients with Fabry disease (developed by a Fabry Expert Panel of United States Fabry specialists [30]). In line with the recommendations for initiation and cessation of ERT developed by the European Fabry working group [25], these treatment guidelines indicate that ERT should be considered in asymptomatic classical males before adulthood (<18 years)." [Initiation of Enzyme Replacement Therapy, p. 420]

Thank you again for providing an opportunity to provide comments. If you have any questions please do not hesitate to contact us.

Sincerely,

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September 19, 2019

Oregon Health Authority  
P&T Committee

RE: Deflazacort for Duchenne Muscular Dystrophy

To Whom It May Concern:

We are the Neuromuscular clinicians in the only Muscular Dystrophy Association supported pediatric multidisciplinary neuromuscular clinic in Oregon. Dr. Finanger, the program director, has fellowship training in Neuromuscular Medicine and is board certified in Neurology and Neuromuscular Medicine. Both Dr. Finanger and Ms. Leach each have more than 15 years of experience caring for individuals with Duchenne muscular dystrophy (DMD). In this clinic we actively follow 65 patients with DMD.

Duchenne muscular dystrophy is a severe genetic condition caused by mutations in the *dystrophin* gene. This gene is an x-linked genetic disorder characterized by the progressive loss of skeletal muscle and degeneration, primarily in boys. It affects one out of 5000 live male births in the US (Mah, 2014; Mendell, 2012). The average age at diagnosis is approximately five years (Ciafaloni, 2009), but delays in motor milestones (such as sitting, standing independently, climbing, and walking) can occur much earlier (Bushby, 2010). Children with Duchenne lose the ability to walk independently and most become reliant on wheelchairs for mobility by the age of 13 (Bello, 2015). Standard medical management of Duchenne requires the use of corticosteroids as well as respiratory, cardiac, orthopedic, and rehabilitative interventions aimed at the sequela that progressively worsen throughout the lifespan of Duchenne (Birnkranz, 2018). Corticosteroids have proven to slow the progression of muscle weakness and delay some of the complications of Duchenne (Bushby, 2010).

In our clinic, we recommend steroids for all patients with DMD and muscle weakness. We base the specific corticosteroid recommendation on the individual patient characteristics. It is our medical opinion that deflazacort should be available as a first line therapy for patients with Duchenne.

**Deflazacort has been shown to be more effective in improving functional outcomes and treating Duchenne muscular dystrophy with fewer side effects than prednisone.**

Results from a large prospective cohort study of the long-term effects of glucocorticoids in patient with Duchenne muscular dystrophy show that the age at loss of ambulation was 2.7 years more delayed in the deflazacort-treated patients than in the prednisone-treated patients (McDonald, 2018). In addition, the American Academy of Neurology (AAN) guidelines on corticosteroid treatment of DMD agrees that deflazacort has been shown to delay the age of loss of ambulation compared to prednisone and has a demonstrated increased survival at 5 and 15 years of follow-up



(Gloss, 2016). Thus, when treated with deflazacort, patients with DMD have a slower decline in function, improved functional outcomes, and increased survival than those taking prednisone.

The AAN guidelines for corticosteroid treatment in DMD recognize that adverse events of weight gain and cushingoid appearance may occur more frequently with prednisone (Gloss, 2016). In a randomized, double blind study comparing deflazacort and prednisone in DMD, weight gain was significantly higher in the prednisone-treated patients (Dubowitz, 2000). In a separate randomized, double-blind study of DMD patients treated with either deflazacort or prednisone, treatment with deflazacort seemed to cause fewer side effects vs prednisone, particularly weight gain (Bonifati, 2000). This finding has also been replicated in additional studies (Griggs 2016, Karimzadeh 2012). The evidence shows that patients with DMD gain significantly more weight when taking prednisone than deflazacort and the weight gain occurs early in treatment. Given this finding, clinically it makes more sense to start with deflazacort to prevent the weight gain associated with prednisone use, particularly as increased weight leads to decreased functional ability and earlier loss of ambulation.

**We appreciate** that the Oregon Health Authority has approved the use of deflazacort and expanded the approved age range to include children over 2 years. It is absolutely necessary that patients with DMD are maintained on corticosteroids. **We appreciate** that OHA has approved deflazacort for patients who do not tolerate prednisone. However, we request that deflazacort be permitted to be considered as a first line option in DMD, given our clinical experience and multiple independent reports (Gloss 2016, McDonald 2018, Shieh 2018) suggesting superior efficacy compared to prednisone.

Thank you for the opportunity to share our clinical experience and your continued partnership to provide excellent care for pediatric neuromuscular patients in Oregon.



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September 19, 2019

Oregon Health Authority  
P&T Committee

RE: Eteplirsen for Duchenne Muscular Dystrophy

To Whom It May Concern:

We are the Neuromuscular clinicians in the only Muscular Dystrophy Association supported pediatric multidisciplinary neuromuscular clinic in Oregon. Dr. Finanger, the program director, has fellowship training in Neuromuscular Medicine and is board certified in Neurology and Neuromuscular Medicine. Both Dr. Finanger and Ms. Leach each have more than 15 years of experience caring for individuals with Duchenne muscular dystrophy (DMD). In this clinic we actively follow 65 patients with DMD, 7 of whom have specific mutations that are amenable to exon 51 skipping.

Duchenne muscular dystrophy is a severe genetic condition caused by mutations in the *dystrophin* gene. This gene is an x-linked genetic disorder characterized by the progressive loss of skeletal muscle and degeneration, primarily in boys. It affects one out of 5000 live male births in the US (Mah, 2014; Mendell, 2012). The average age at diagnosis is approximately five years (Ciafaloni, 2009), but delays in motor milestones (such as sitting, standing independently, climbing, and walking) can occur much earlier (Bushby, 2010). Children with Duchenne lose the ability to walk independently and most become reliant on wheelchairs for mobility by the age of 13 (Bello, 2015). Standard medical management of Duchenne requires the use of corticosteroids as well as respiratory, cardiac, orthopedic, and rehabilitative interventions aimed at the sequela that progressively worsen throughout the lifespan of Duchenne (Birnkrant, 2018). Eteplirsen is the only FDA-approved therapy to treat the underlying genetic cause for Duchenne Muscular Dystrophy.

The most frequent mutation in DMD is a deletion. Deletions may result in either an out of frame mutation, closing the reading frame and producing no dystrophin, or an in frame mutation, resulting in a truncated dystrophin and associated with the less severe form of this condition, Becker muscular dystrophy. Exon skipping is a strategy involving splice-switching oligomers, changing an out of frame mutation (with no dystrophin production) to an in frame mutation (with truncated dystrophin production). 13% of all Duchenne patients have a genetic deletion amenable to skipping exon 51 (Aartsma-Rus, 2009). Eteplirsen alters splicing of the dystrophin gene which results in an in frame dystrophin transcript and a shorter, but functional protein (Cirak 2011, Charleston 2018). The initial study as well as long-term follow up studies of patients on eteplirsen show prolonged duration of ambulation, preservation of pulmonary function, and increased dystrophin expression on western blot (Kinane 2018, Mendel 2013, Mendel 2016, Charleston 2018). Dystrophin expression by western blot increased to 0.44% after 48 weeks and 0.93% after 180 weeks of exposure to eteplirsen (Charleston 2018) reinforcing the importance of continued use of eteplirsen. Similarly low levels of dystrophin have been shown to be sufficient in significantly prolonging ambulation (Waldrop 2018). While this



publication only reports on a single patient, a more recent analysis of 77 patients with DMD in Europe showed that individuals with dystrophinopathies who have minimal residual dystrophin production (>0% - <5%) had a statistically significant increase in duration of ambulation compared to those with 0% dystrophin production (Amthor 2019), confirming that residual dystrophin, even in small quantities, mitigates dystrophinopathy towards milder phenotypes.

We appreciate the opportunity to use eteplirsen in patients amenable to exon 51 skipping. However, it appears that the list of approved mutations is not complete. There are 43 additional mutations amenable to exon 51 skipping that are not included in the PA criteria (full list provided below).

We support the use of eteplirsen for patients with Duchenne muscular dystrophy who have mutations amenable to exon 51 skipping. In addition, we continue to participate in the ongoing Phase 3 clinical trial evaluating the long-term efficacy of eteplirsen and look forward to reviewing the results of this trial with you once available.

Thank you for the opportunity to share our clinical experience and your continued partnership to provide excellent care for pediatric neuromuscular patients in Oregon.



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Deletions amenable to exon 51 skipping:

3-50	14-50	25-50	33-50	41-50	52
4-50	15-50	26-50	34-50	42-50	52-58
5-50	16-50	27-50	35-50	43-50	52-61
6-50	17-50	28-50	36-50	45-50	52-63
9-50	19-50	29-50	37-50	47-50	52-64
10-50	21-50	30-50	38-50	48-50	52-66
11-50	23-50	31-50	39-50	49-50	52-76
13-50	24-50	32-50	40-50	50	52-77

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September 19, 2019

Oregon Health Authority  
P&T Committee

RE: Nusinersen for Spinal Muscular Atrophy

To Whom It May Concern:

We are the Neuromuscular clinicians in the only Muscular Dystrophy Association supported pediatric multidisciplinary neuromuscular clinic in Oregon. Dr. Finanger, the program director, has fellowship training in Neuromuscular Medicine and is board certified in Neurology and Neuromuscular Medicine. Both Dr. Finanger and Ms. Leach each have more than 15 years of experience caring for individuals with Spinal Muscular Atrophy (SMA). To date, we have had the opportunity to clinically treat 24 patients with nusinersen.

We appreciate the inclusion of patients with SMA types 1, 2 or 3 for treatment with nusinersen. Our clinical experience supports the continued use of this medication for all three subtypes and have documented both motor and pulmonary improvements as well as an improvement in quality of life for the vast majority patients.

The renewal criteria state that testing of motor function must demonstrate "improvement from baseline motor function score documented within one month of renewal request AND more areas of motor function improved than worsened". This criteria appears to be directly only at the Hammersmith Infant Neurologic Exam (HINE) measure used in the phase 3 clinical trial of nusinersen in infantile-onset SMA (ENDEAR). It would be more clinically appropriate to modify these criteria to allow for improvement in motor function testing or stabilization of motor function. In addition, while functional motor outcomes are an important factor in follow up of patients with SMA, they do not assess other aspects affecting health-related quality of life including factors such as participating in activities, respiratory function and physical impairment. Thus, we would recommend a more inclusive assessment of efficacy, which includes stabilization of motor function as well as documentation of other benefits of gaining specific motor skills, such as independence or the ability to self-care.

Thank you for the opportunity to share our clinical experience and your continued partnership to provide excellent care for pediatric neuromuscular patients in Oregon.

Erika Finanger, MD MS  
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September 19, 2019

Oregon Health Authority  
P&T Committee

Doernbecher Children's  
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RE: Onasemnogene abeparvovec-xioi for Spinal Muscular Atrophy

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To Whom It May Concern:

Yoon-Jae Cho, MD  
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We are the Neuromuscular clinicians in the only Muscular Dystrophy Association supported pediatric multidisciplinary neuromuscular clinic in Oregon. Dr. Finanger, the program director, has fellowship training in Neuromuscular Medicine and is board certified in Neurology and Neuromuscular Medicine. Both Dr. Finanger and Ms. Leach each have more than 15 years of experience caring for individuals with Spinal Muscular Atrophy (SMA).

Stephen Back, MD, PhD  
Professor of Neurology &  
Pediatrics

We have reviewed the OHA proposed guidelines for the use of onasemnogene abeparvovec-xioi for the treatment of spinal muscular atrophy. We look forward to partnering with OHA to provide ongoing clinical data regarding onasemnogene abeparvovec-xioi via the stipulated case management, including follow-up assessment to assess treatment success, monitoring, and adverse events.

Barry Russman, MD FAAP,  
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Doernbecher  
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September 18, 2019

Pharmacy and Therapeutics Committee  
Oregon Health Authority

Dear Members of the Oregon Pharmacy and Therapeutics Committee:

On behalf of patients and families living with cystic fibrosis (CF), we write to commend Oregon Medicaid for recommending updating the prior authorization criteria to reflect recent label expansions for ivacaftor (Kalydeco®) and tezacaftor/ivacaftor (Symdeko®). Evidence indicates that early treatment with CFTR modulators has the possibility to slow or even reverse early organ damage which characterizes the disease.

#### **About the Cystic Fibrosis & the CF Foundation**

Cystic fibrosis is caused by genetic mutations that result in the malfunction of a protein known as the cystic fibrosis transmembrane conductance regulator (CFTR). Decreased CFTR protein function causes organ damage and the associated symptoms of cystic fibrosis and leads to early death, usually by respiratory failure. As the world's leader in the search for a cure for CF and an organization dedicated to ensuring access to high quality, specialized CF care, the Cystic Fibrosis Foundation accredits 123 care centers, including 4 in Oregon, and 55 affiliate programs nationally that provide multidisciplinary, patient-centered care in accordance with systematically reviewed, data-driven clinical practice guidelines. Treatment options for this rare, life-threatening disease are limited.

#### **About CFTR Modulators**

Ivacaftor, lumacaftor/ivacaftor, and tezacaftor/ivacaftor are FDA-approved therapies that improve the function of CFTR protein for individuals with specific mutations in the *CFTR* gene. CFTR modulators mark a significant advance in treatment of cystic fibrosis as patients with CF have a fundamental medical need for correction or potentiation of the CFTR protein. For those with an eligible mutation, CFTR modulator therapies target the underlying cause of cystic fibrosis rather than addressing the symptoms and clinical manifestations. CFTR modulator therapies present an opportunity to preserve health and lung function in eligible individuals with CF by slowing the progression of the disease and preventing costly hospitalizations, declining health status, deteriorating quality of life, and premature death.

Different *CFTR* mutations cause different defects in the protein; therefore, modulators are effective only in people with specific mutations. Ivacaftor is indicated for those 6 months and older with one mutation in the *CFTR* gene that is responsive to ivacaftor. Tezacaftor/ivacaftor is indicated for those 6 years and older with two copies of *F508del* mutation or at least one residual function mutation in the *CFTR* gene as indicated on the FDA label.<sup>1</sup> Tezacaftor/ivacaftor is a therapeutic alternative to lumacaftor/ivacaftor but does not have the same adverse side effects such as chest-tightness or drug-

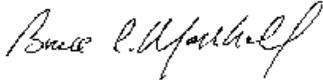
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<sup>1</sup> Eligible mutations include: E56K, R117C, A455E, S945L, R1070W, P67L, E193K, F508del (two copies), S977F, F1074L, R74W, L206W, D579G, F1052V, D1152H, D110E, R347H, 711+3A→G, K1060T, D1270N, D110H, R352Q, E831X, A1067T, 2789+5G→A, 3272-26A→G, 3849+10kbC→T

drug interactions. This drug is also a therapeutic alternative for some individuals with residual function mutations currently eligible for ivacaftor.

We stand ready to answer any questions about CFTR modulator therapies. We would be happy to connect you with local CF experts to further discuss this important issue. Please contact Jackie Erdo, MPH, Manager of Policy and Advocacy, at [jerdo@cff.org](mailto:jerdo@cff.org) or 301-841-2628.

Sincerely,



Bruce C. Marshall, MD  
Senior Vice President of Clinical Affairs



Lisa Feng, DrPH  
Senior Director of Policy and Advocacy



# Fabry Support & Information Group

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Drug Use Research & Management Program  
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9/23/2019

Dear Oregon Pharmacy & Therapeutics Committee,

My name is Jack Johnson. I am a Fabry patient, founder and Executive Director of the Fabry Support & Information Group (FSIG), a national nonprofit organization formed in 1996 and dedicated to the needs of the Fabry disease community. I am also Vice President, Americas and Global of the Fabry International Network (FIN). Regrettably I am unable to attend the Oregon Drug Use Review / Pharmacy & Therapeutics Committee meeting in person so am submitting this testimony for consideration.

I thank you for the opportunity to address the issues surrounding treatment of this rare, devastating, progressive and life threatening condition. While periodic review to ensure and update approved, established treatment guidelines to maximize therapeutic benefit is advantageous. It is of extreme concern to find verbiage potentially rejecting the only Food and Drug Administration (FDA) drugs approved to treat the underline cause of Fabry disease. All other symptom based treatment modes are by their nature reactive, piecemeal and at a minimum without any hope of arresting disease progression.

The medical books, published papers and clinical trial reports explain the biological aspects, but let me tell you about the lives of those impacted by Fabry. Many have the blessing of outwardly appearing relatively healthy but have the curse to feel very much the opposite. They may suffer daily pain that is difficult to adequately explain and all too often easily discounted by others. Even severe pain crises, which can make your world come to a stop until it passes or some relief can be found, are often not appreciated.

Living around where the nearest bathroom is can contribute to make a social life with family or friends seem a difficult dream. Frequent medical appointments or trips to the Emergency Room on top of the difficulties of day-to-day life with a chronic condition can significantly interrupt school or work. Hearing loss even with assistive amplification results in increasing isolation from family and friends. Transient ischemic attack or stroke can leave victims asking themselves daily, will it happen again today. The psychosocial burden of this deteriorating existence without any real hope of stabilization or improvement cannot be overstated.

Prior to 2003 US Fabry patients had a bleak prognosis of disease progression to end organ failure at some unknown point. Physicians could prescribe pills for a number of symptoms like pain or cardiac arrhythmia. Dialysis and transplant for end stage renal failure. In some cases cardiac transplant was needed to forestall mortality. Then Enzyme Replacement Therapy (ERT) became available. Hope for the future became a reality.

Tragically a drug shortage occurred in 2009. One result of drastically reduced or no ERT was return of symptoms. Pain, fatigue, gastrointestinal, and other symptoms where being reported. FIN conducted an international survey of Fabry patients cataloging the aforementioned outcomes. These patient reported outcomes were not documented by FIN alone. Reported changes were also documented by treating Fabry expert physicians. Those experiences resulted in an EMEA report. Assessment report on the shortage of Fabrazyme' Overview of Shortage Period: Spontaneous Reports from June 2009 through 15 September 2010 and Registry Data from June 2009 through 05 August 2010. This report and a poster prepared from the FIN survey data are attached for review. In the interest of time the EMEA report conclusions are on pages 7 and 8.

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Another area of significant concern expressed by patients and physicians alike was for some the return of infusion associate reactions. Most patients experiencing this were able to retolerize but not all leaving them without an ERT option. These outcomes highlight the absolute necessity of maintaining uninterrupted treatment. While no interruption of treatment utilizing Migalastat has been reported to my knowledge similar outcomes may be possible.

It is bewildering to say the least that the very FDA report released by the administration when drug approval was granted for agalsidase beta is now being utilized as a primary argument to recommend discontinuing its use. A drug that received and maintains approval from the nation's highest authority on medical scrutiny.

Any failure to support continued administration of approved drugs for the treatment of Fabry disease is in short a step backward. Those Fabry expert physicians treating and the vast majority of patients receiving treatment will agree.

It is in the best interest of all concerned that the Oregon Pharmacy & Therapeutics Committee final conclusion is that those afflicted with Fabry disease continue to receive the established highest standard of care available for this progressive, treatable condition. FSIG and Oregon's Fabry patient population await your decision.

Respectfully,

A handwritten signature in cursive script that reads "Jack Johnson".

Jack Johnson,  
Executive Director



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

## Assessment report

for

**FABRAZYME**

**agalsidase beta**

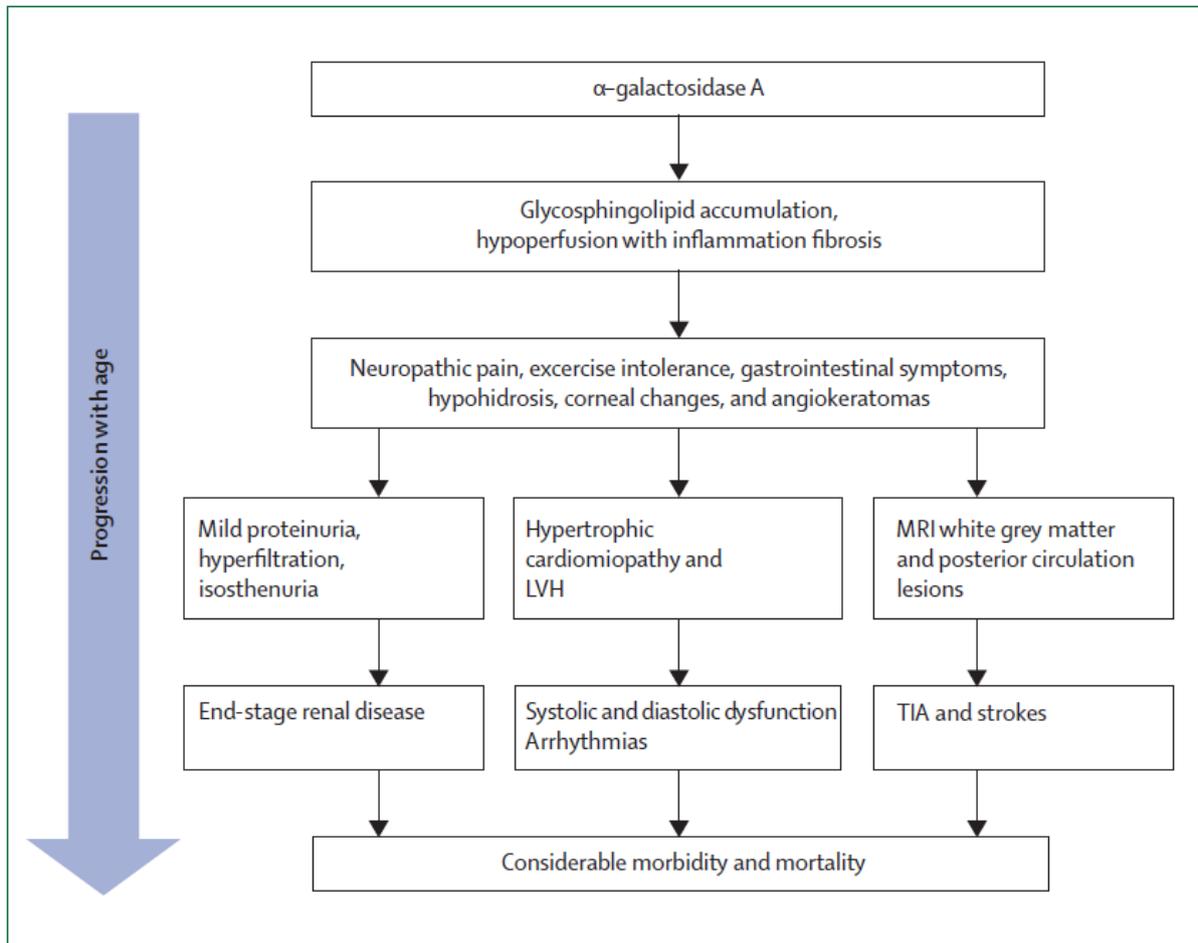
**Assessment report on the shortage of Fabrazyme'  
Overview of Shortage Period: Spontaneous Reports from June 2009 through 15  
September 2010 and Registry Data from June 2009 through 05 August 2010**

**EMA/H/C/000370**



## I. INTRODUCTION

Fabry's disease is a lysosomal storage disorder due to a deficiency in alpha-galactosidase A. The natural course of the disease is illustrated in figure 1.



**Figure 1: Progression of clinical findings in Fabry's disease with age**

Progression of any of the paths depicted can proceed independently from the others, which means that for some patients, cardiac disease will be the most severe whereas for others renal or CNS disease can predominate. LVH=left ventricular hypertrophy. TIA=transient ischaemic stroke.

**(Zarate & Hopkin. Lancet 2008;372:1427-35)**

At the start of the disease (during the first decades of life), the main manifestations are pain (crises) and gastrointestinal symptoms. The long-term progression of Fabry disease is associated with chronic renal disease, cardiovascular disease, and cerebrovascular events (during fifth decade of life); this deterioration is a major cause of morbidity and mortality.

Fabrazyme® is an enzyme replacement therapy for Fabry's disease. The recommended dose and frequency in section 4.2 of the SmPC is 1 mg/kg every other week (eow).

Since June 2009 there has been a shortage of supply of Fabrazyme (agalasidase beta) because of production and quality (GMP) problems. To date four Direct Healthcare Professional Communications (DHPCs) with dose recommendations have been released in the European Union (EU):

25 June 2009:

- Children and adolescents less than 18 years old as well as adult male Fabry patients to continue with recommended Fabrazyme dosing and frequency.
- Adult female Fabry disease patients with no evidence of clinically significant end organ damage to be treated with a reduced dose of 0.3-0.5 mg/kg every 2 weeks.

#### 28 September 2009:

- Children and adolescents less than 18 years old to continue with recommended Fabrazyme dosing and frequency.
- Adult male patients already treated and stabilized to receive 0.3 mg/kg every 2 weeks (as for adult female patients).
- Patients should be followed up every two months, and plasma or urinary globotriaosylceramide (GL-3) levels should be closely monitored.
- Patients who demonstrated a deterioration of disease should be switched back to their original dosage regimen with Fabrazyme.

#### 22 April 2010:

- Treatment recommendations as communicated in the DHPC of September 2009 remained in place.
- For patients experiencing aggravation of disease symptoms and/or AEs ascribed to the lowered dose of Fabrazyme, physicians were advised to switch their treatment back to their original dosing regimen or initiate treatment with an alternative approved medicinal product.

#### 09 July 2010:

- No new patients should be started on Fabrazyme, if alternative treatment is available.
- For patients on a dose lower than the recommended dose, physicians should consider switching to an alternative treatment, such as Replagal.
- Where alternative treatment is not available or where (continuation of) treatment with Fabrazyme is deemed medically necessary, it is important to note that an increase in clinical manifestations indicative of Fabry disease progression has been observed with the lowered dose.

In the United States all patients were asked to reduce their Fabrazyme use by spreading out their usual dose over a longer period of time.

During the shortage period, the MAH has updated the Rapporteur with reports on spontaneous reporting and data from the Fabry registry. These data and the Rapporteur's conclusions are summarized in this assessment report.

On 4 and 9 October 2010 a consensus meeting took place of representatives of physicians treating Fabry disease in the EU. At that meeting treatment recommendations in times of shortage were agreed. A representative of the EMA was present as an observer.

The purpose of this assessment report is to present an overview of the data received so far on patients on a lower dose of Fabrazyme.

## **II. POSSIBLE DETERIORATION IN PATIENTS ON THE LOWERED DOSE**

The Rapporteur has reviewed all data from spontaneous reports regarding patients who reported adverse events (AEs) assessed to be suggestive of clinical deterioration on a lowered dose of Fabrazyme (from Genzyme's Global Patient Safety and Risk Management department (GPS&RM) database) for the period from 25 June 2009 through 15 September 2010.

In addition, all information from the Fabry Registry regarding certain clinical characteristics of patients whose doses of Fabrazyme were lowered during a period of approximately 13 months, from 25 June 2009 through 05 August 2010 have been reviewed and the data from both sources have been compared.

In all cases, it was assumed that these patients' doses were lowered in response to the reduction in the global supply of Fabrazyme during this period.

The MAH considered the following:

A. All spontaneous cases reported to GPS&RM and medically reviewed from 25 June 2009 through 15 September 2010 were considered for the analysis of patients experiencing clinical deterioration on a lower dose of Fabrazyme if they met the following three criteria:

1. The reported AE occurred after 25 June 2009,
2. The patient was on a lowered dose of Fabrazyme due to the supply shortage, and
3. The AE was not an infusion associated reaction (IAR).

B. After selecting the cases that met these criteria, the narratives were screened by the MAH for information with regard to evidence of clinical deterioration. A medical review of these cases, which included all relevant medical history and available laboratory data, was performed by GPS&RM to determine whether the AEs were suggestive of potential clinical deterioration. Due to the ongoing limited supply, cases of patients with clinical deterioration but without complete documentation of a lowered dose have also been incorporated into the reports; further efforts are being made with the patient's health care professional (HCP) to confirm the dose reduction in these cases.

C. Events assessed to be suggestive of potential clinical deterioration after medical review included, but were not limited to: cardiovascular events such as arrhythmia, coronary artery disease or heart failure; cerebrovascular events such as transient ischaemic attacks or cerebrovascular accidents; renal events such as renal impairment or renal failure; gastrointestinal events such as abdominal pain, nausea, vomiting, and diarrhoea; events consistent with Fabry disease-related pain such as paraesthesias, pain in extremities, or peripheral neuropathy; changes in hearing; and constitutional symptoms such as fatigue and malaise.

Physicians who enrol patients in the Fabry Registry are asked to monitor patients and submit clinical data according to a Minimum Recommended Schedule of Assessments. This schedule includes key clinical and laboratory parameters that should be evaluated and the frequency at which they should be reported to the Fabry Registry. However, Genzyme has found that these data are typically entered on a semi-annual or annual basis. In addition, not all changes in dosage have been reported to the Fabry Registry and changes in the average reported dose may not accurately reflect patients' actual treatment regimens.

Events of chronic renal disease, cardiovascular disease, cerebrovascular events, and deaths reported to the Fabry Registry were investigated in patients whose doses were lowered during the period from 25 June 2009 through 05 August 2010. In addition, data related to peripheral pain, abdominal pain, and diarrhoea were included. Reported plasma and urine levels of GL-3 were also analyzed in patients who are enrolled in the Fabry Registry.

### **III. REVIEW OF DATA FROM SPONTANEOUS REPORTS**

The MAH submits bi-weekly reports on patients all over the world. Most reports are on non-EU patients. In every report, the MAH is required to discuss the EU patients separately.

In the EU, of the patients on Fabrazyme, approximately 4% was on a dose lower than 1 mg/kg/eow prior to the start of the supply shortage.

After a decline, the number of patients on Fabrazyme as well as the number of patients on the lowered dose seems to have stabilized. This is an indication that the recommendations are being followed to some extent and that no or a small number of new patients are being initiated on Fabrazyme.

In the figure below, the bars indicate the numbers of reported AEs. The figure only presents the unique patients, so the real number of AEs is higher because for some patients there are more AE reports in time received. There appears to be a stabilisation in the number of AEs, suggesting that patients who still are on the lowered dose, are relatively stable and are not adversely affected by the use of the lowered dose.

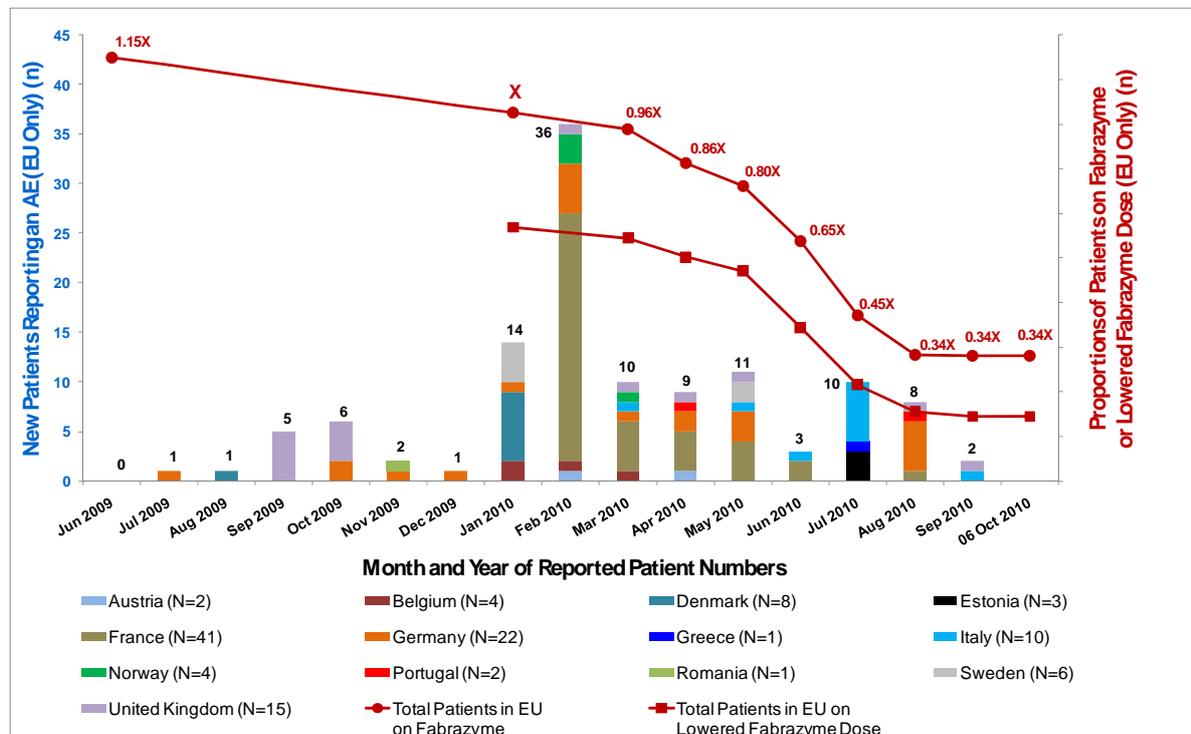
See table 1 and figure 2 below.

**Table 1: Estimated Percentage of Patients in the European Union on a Lower Dose**

Estimated Number of:	January 2010	March 2010	April 2010	May 2010	June 2010	July 2010	August 2010	Sept. 2010	06 Oct. 2010
Patients on Fabrazyme*	x	0.96x	0.86x	0.80x	0.65x	0.45x	0.34x	0.34x	0.34x
Patients on 1 mg/kg/eow	26%	26%	25%	23%	31%	37%	37%	41%	41%
Pediatric patients on 1 mg/kg/eow	5%	5%	5%	5%	5%	6%	7%	7%	7%
Patients on 0.5 mg/kg/eow	32%	22%	23%	22%	21%	6%	13%	12%	12%
Patients on 0.3 mg/kg/eow	36%	47%	47%	50%	43%	51%	42%	40%	40%

\*Note that x=total number of patients on Fabrazyme per January 2010 (exact number not disclosed for confidentiality reasons). In time, this number gradually decreases.

**Figure 2 New Unique Patients Reporting AEs Assessed to be Potentially Suggestive of Clinical Deterioration on a Lowered Dose of Fabrazyme by Country, and Proportions of Patients on Fabrazyme and Lowered Doses of Fabrazyme (EU Patients Only) Since the Start of the shortage**



\* Bar graph data in Figure 1 represent the total number of unique patients by month who are new to the analysis of case reports assessed to be suggestive of potential clinical deterioration on a lowered dose of Fabrazyme. All patients new to the analysis during the current biweekly period are presented in that month. However, in subsequent reports, the patients will be listed in the month of the worldwide receipt date (WWRD) of their AE report. For example, if a case was initially reported with a WWRD in February 2010, but the data confirming that the patient was on a lowered dose were not received and medically reviewed until 20 September 2010, the case would be presented for the first time in the 16 September 2010 through 30 September 2010 biweekly report in the column for 16-30 September 2010. This presentation shows how many new unique patients from the EU are reporting AEs assessed to be suggestive of clinical deterioration on a lowered dose of Fabrazyme during the recent biweekly period. However, in subsequent reports, the case would be presented in the February 2010 column based on the initial WWRD to the safety database. Further, each unique patient is counted in Figure 1 only once. Therefore, if a patient reports one AE in September 2009 and another separate AE in March 2010, the patient will be included in the calculations for September 2009 only.

\*\* The AEs received and medically reviewed after 30 September 2010 are beyond the scope of this document and will be presented in future reports.

There is a clear trend of increasing reports of (serious) AEs since the shortage. The higher the percentage of patients receiving the lowered dose, the higher the number of AEs reported. After the recommendations to switch to Replagal or to return to a higher dose when clinical deterioration appeared, this percentage decreased, as well the absolute number of reports. A subgroup of patients seems to be doing well on the lower Fabrazyme dose.

The MAH did not provide comparable data for the period before the shortage and concluded that based on the limited data available, it is not possible to ascertain whether more patients are having serious clinical events while on lowered doses of Fabrazyme, compared with earlier data from patients on a full dose of Fabrazyme.

However, the MAH did provide and compare quarterly data from Q3 2009 (see table 1). The percentage of AEs ascribed to the lowered dose increased steeply. After the increase in AEs seen from Q4 2009 to Q1 2010, the number of reported AEs from Q1 2010 to Q2 2010 appears to have been either stabilizing or decreasing.

Over time, increases have been seen in serious cardiac and nervous AEs and, to a lesser extent, in renal events, while a decrease, albeit less steep, has been seen in reported AEs related to pain/pareasthesias.

The reported AEs are summarised in table 2. This table concerns data up to Q3 2010.

Note that this table presents worldwide data.

**Table 2 Summary of Patients and Adverse Events Spontaneously Reported to Genzyme's Global Patient Safety & Risk Management Database That Were Received and Medically Reviewed from 25 June 2009 through 30 September 2010 and Assessed as Being Suggestive of Clinical Deterioration while on a Lowered Dose of Fabrazyme (selection of SOCs)**

Adverse event category Preferred Term	Q3 2009 (N=21)		Q4 2009 (N=34)		Q1 2010 (N=89)		Q2 2010 (N=90)		Q3 2010	
	Events (n)	Patients (n)	Events (n)	Patients (n)	Events (n)	Patients (n)	Events (n)	Patients (n)	Events (n)	Patients (n)
Cardiac disorders (arrhythmias, cardiac failure, cardiac occlusion, MI)	1	1	1	1	13	12	14	14	11	10
Cerebrovascular- stroke	1	1	2	2	7	7	2	2	10	7
Fabry disease related pain	10	9	10	9	41	41	35	35	24	21
Gastrointestinal pain	2	2	5	5	3	3	5	4	7	7
Gastrointestinal diarrhoea	2	2	5	5	5	5	4	4	1	1
Renal disorders (renal failure, renal failure chronic)	-	-	-	-	6	6	4	4	9	9

# The above data come from: a) Genzyme's "Report on Fabry Registry Patients who received Fabrazyme Dose reductions between 25 June 2009 and 05 August 2010 and Comparison to Spontaneous reports to Global Patients Safety and Risk Management Database" dated 23 September 2010; b) data from the third quarter 2010 (obtained from the biweekly reports 01-15 July; 16-31 July; 01-15 August; 16-31 August; 01-15 September; 16-30 September 2010).

#### *Patients returning to higher dose or switched to Replagal*

Some information was received on patients who had been switched to Replagal. However, the data is limited and no conclusions can be drawn from them.

There were also switches between Replagal and Fabrazyme prior to the Fabrazyme supply shortage.

#### *GL-3 levels*

There are some data available on GL-3 levels measured in patients before and after their dose lowering. These data do not show any clear trend.

## **IV. REVIEW OF DATA FROM FABRY REGISTRY**

In the Fabry Registry, 410 patients were reported to be on lowered dose (US 59% and Europe 22%).

As of 5 August 2010, the Registry had enrolled a total of 3,681 Fabry patients (1,808 males and 1,873 females), irrespective whether or not they received enzyme replacement therapy.

Cerebrovascular events: The stroke incident rates have increased slightly since 25 June 2009 (from 0.63 (95% CI: 0.31–1.12) per 100 person years of follow-up to 1.32 (95% CI: 0.36–3.37).

Renal events: Since the previous Registry report, one new case of a renal event was reported (initiation of chronic dialysis). The incidence rate in these very small numbers did not increase during the shortage.

Cardiovascular events: The number of patients who had cardiovascular events after 25 June 2009 was small (N=3) and the observation period was short. Therefore, no conclusion can be made on whether or not there is any meaningful difference in the incidence of cardiovascular events in Fabrazyme-treated patients before and after 25 June 2009.

Neurologic peripheral pain, abdominal pain, diarrhoea: There have been consistent reports of a higher percentage of patients reporting peripheral pain, abdominal pain and diarrhoea on a daily basis after 25 June 2009, compared with the period before that date.

Globotriaosylceramide (GL-3) levels: The findings on the plasma GL-3 data are comparable with those in the spontaneous reporting; there is no apparent change.

Regarding urine GL-3 levels, six of the seven patients had lower levels post June 2009 compared with pre June.

## **V. CONSENSUS MEETING**

On 4 and 9 October 2010, a consensus meeting of treating physicians was held. The purpose of that meeting was to reach consensus on the proper management of Fabry disease during the period of shortage of enzyme replacement therapy (ERT) and to come up with clear treatment recommendations for physicians during the shortage period of Fabrazyme (shortage of agalsidase beta and subsequent constraints in supply of agalsidase alfa). The aim was also to have the agreed treatment recommendations published in a scientific journal.

The EMA was present as an observer and the CHMP was informed of the outcomes of the meeting by the physicians' representative.

The CHMP took the outcome of this consensus group of experts into account.

## **VI. CONCLUSIONS**

- There is a clear trend of increasing reports of (serious) AEs since the start of the shortage. The higher the percentage of patients receiving the lowered dose, the higher the number of AEs reported. After the recommendations to switch to Replagal or to return to a higher dose when clinical deterioration appeared, this percentage, as well the absolute number of reports, decreased. This provides a picture of more and more patients at risk from the lowered dose switching back to higher dose or to Replagal.
- A certain patient subgroup seems to have no obvious clinical effects due to the lowered dose.
- The safety data on the registry period June 2009 to 05 August 2010 confirm the trends as seen in the spontaneous reports. Due to its voluntary-based and periodic reporting, the Registry is somewhat 'behind' in time and this is reflected in the data. In the Registry so far the increases and decreases described above are still developing.

- Taking into account the potential for increased awareness of the supply shortage among healthcare providers which could potentially lead to reporting biases, the limitations of spontaneous reporting and the small number of reports, there is an increase in reporting of adverse events possibly due to the lowered dose. In the early stages of the shortage the main increases in AEs were related to pain/paresthesia events, while later on in the shortage period, the main increases were in serious cardiac events such as myocardial infarction, in serious nervous disorders such as stroke, and – possibly to a lesser extent – in renal disorders. There have been consistent reports of a higher percentage of patients reporting peripheral pain, abdominal pain and diarrhoea on a daily basis after 25 June 2009 (start of the shortage).
- **This pattern of adverse events resembles the natural, but accelerated, course of Fabry's disease.**
- The CHMP requests the MAH to include this important data on long-term low dosage use in the SPC in section 5.1. The MAH should provide wording stating that during the shortage period, spontaneous reports on the following adverse events (indicating a deterioration of the disease) were received: Fabry disease-related pain, paresthesia, diarrhoea, cardiac disorders as arrhythmias and myocardial infarction, nervous system disorders as stroke, and renal disorders as renal failure.
- A yet unexplained finding is that the plasma GL-3 levels show no apparent change before and after dose lowering. Data on the urine GL-3 levels are scarce; in six of the seven patients there was a lowering after dose lowering.



# The Fabry International Network (FIN) Fabry Treatment Survey

[www.fabryintnetwork.com](http://www.fabryintnetwork.com)

Megan Fookes<sup>a</sup>, Jack Johnson<sup>b</sup>, Dennis Østergaard Pedersen<sup>c</sup>, Christine Lavery<sup>d</sup>, Kees Bosman<sup>e</sup>, Lut De Baere<sup>f</sup>, Anna Meriluoto<sup>g</sup>, Erica Schenk<sup>h</sup>, Adrian (Ed) & Marlene Koning<sup>i</sup>  
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## Introduction

As a global organization based in the Netherlands the purpose of the FIN Fabry Treatment Survey was to evaluate the largest patient perspective possible concerning the impact of the ongoing Enzyme Replace Therapy (ERT) Fabrazyme® shortage and restricted supply of Replagal®.

## Background

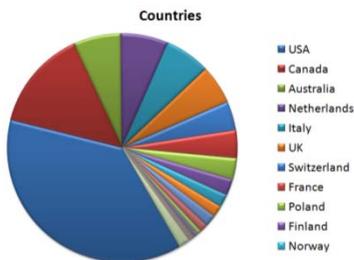
The Fabry Treatment Survey was developed by FIN in collaboration with its Medical Advisory Board (MAB) including input from FIN's three primary sponsors; Amicus Therapeutics, Genzyme/Sanofi and Shire HGT. The survey was conducted in late 2010 – early 2011.

## Methods

- FIN designed an online survey in English.
- It was translated into French, Italian, German, Polish, Portuguese, Spanish and Dutch.
- 27 questions: multiple choice / 3 open ended response.
- The survey was sent to FIN members of 24 organisations in 22 countries.
- The survey was open to all Fabry affected men, women and children without regard to treatment.
- FIN collected responses and translated into English.
- Analysis was completed by professional medical research company.

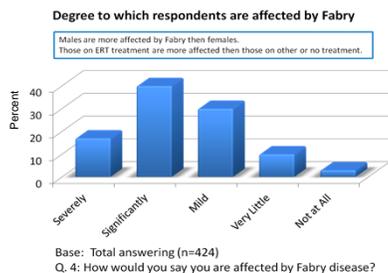
## Respondents by Region

- Responses came from North America 52%, Europe 39% and all other regions 9%
- Response locations were dominated by English speaking regions being; US 39%, Canada 14% and Australia 7%.
- Total number of respondents before deadline was 442
- The mean average age of survey participants was 45 years. Ages ranged from 18 to 65.
- Males and females responded in equal numbers.
- The survey was not distributed in all countries receiving ERT and results may not be representative of the Fabry patient community at large.



## Degree Respondents Where Impacted by Fabry

- Over half of respondents say they are severely or significantly affected by Fabry disease. Few are not affected. Males are more affected by Fabry than females and those on ERT treatments are more affected than those on other or no treatment.



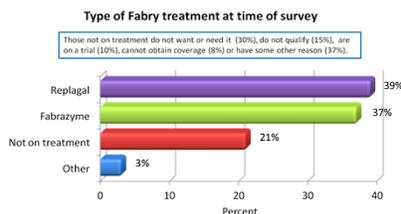
## Fabry International Network



The Fabry International Network (FIN) is an independent nonprofit organisation representing the global Fabry community comprising of 27 member organisations from 24 countries.

## Type of Fabry Treatment at time of survey

- At the time of survey most respondents were on ERT. Those on ERT have been on treatment for a mean of 6 years.



## Impact of Shortage on Health and Well-Being

### Limitations

- In interpreting the positive and negative effects, please note that the base sizes are not the same. About 140 respondents who had a change in medication said they had some sort of negative impact from the change. Only 42 of these same individuals said they had a positive impact and only 14 said they felt better or had fewer symptoms.

### The negative effects since being on reduced dose of Fabrazyme®, transferring to Replagal® or stopping treatment.

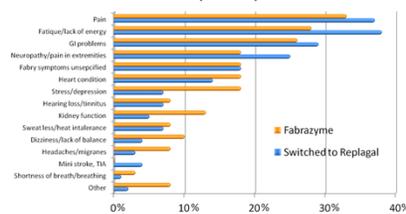
- 21% had no negative effects, 24% had no answer and 55% reported negative effects of those whose treatment was affected. Physical symptoms, especially pain, fatigue, GI problems and neuropathy are the most common problems.

## Whether Any Negative Effects



- Those on Fabrazyme® more often reported a negative effect (65%) than those who switched to Replagal® (51%). However, those with problems reported similar negative effects.

## Type of negative effect from changes in Fabry treatment (unaided)



- A majority of those whose treatment was affected report a negative impact. Physical symptoms, especially pain, fatigue, GI problems and neuropathy, are the most common problems.

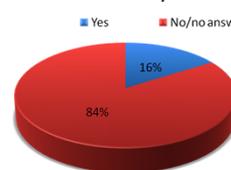
## Positive effects for those on reduced dose of Fabrazyme®

- Very few reported a positive impact after changing treatment. Those on a reduced dose of Fabrazyme® like having more free time. Some who switched to Replagal® reported improved health and shorter infusions.

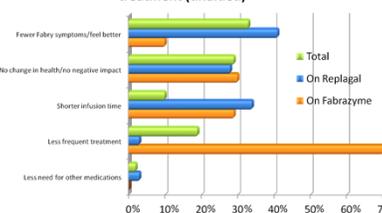
### Participant responses are personal comments.

All treatment decisions should be made with a qualified physician.

## Whether Any Positive Effects



## Type of positive effect from changes in Fabry treatment (unaided)



## Conclusions

- Male patients on ERT were generally more affected by Fabry than females.
- The number of females responding to the survey was equal to the number of males.
- Even though the survey was distributed in seven different languages the predominantly English speaking countries dominated the responses.
- Communication about the supply disruption reached the majority of patients in a reasonable time frame, but improvements could be made.
- Fabry patient organisations did the best job of informing the patient community about the shortage.
- Globally the majority of patients on Fabrazyme® has been on a reduced dose and has missed treatments.
- In the US and some other regions, Replagal® is not commercially available as it is not licensed and therefore unavailable as a form of treatment. The results presented are dominated by responses from the US and Western Europe. Given that response patterns differ greatly by country/region, results should not be considered representative of global experiences.
- The analysis presented is based on a collection of 442 individual responses representing a proportion of the global patient population receiving Fabry treatments, and so has value both as feedback for FIN, Fabry Stakeholders and the Fabry population as a whole. It may also be useful for other groups facing similar difficulties in the future.
- Due to a number of limitation this survey may not be representative of the Fabry patient community as a whole.

FIN thanked all those that responded to the survey providing highly valued insights into personal experiences. The author(s) declare that they have no competing interests.



To: Oregon Health Authority  
Oregon Drug Use Review/Pharmacy & Therapeutics Committee  
Re: Fabry Disease: agalsidase beta (Fabrazyme<sup>®</sup>)

September 26, 2019

Fabry disease is a rare, X-linked genetic disorder caused by a deficiency of the lysosomal enzyme  $\alpha$ -galactosidase A-which leads to accumulation of the substrate globotriaosylceramide or "GL-3".<sup>1</sup>

From birth, patients with Fabry disease experience progressive accumulation of GL-3 within the lysosomes of cells throughout the vascular endothelium. With progression, substrate accumulation eventually results in tissue and organ damage and ultimately leads to the development of significant clinical manifestations.<sup>2</sup> Symptoms of Fabry disease can include neuropathic pain in the extremities, pain crises, GI complications, progressive renal decline, end stage renal disease, cardiac arrhythmias, cardiac failure, and stroke.<sup>3</sup> While severity of symptoms may vary among patients with the same genotype, patients with Fabry disease suffer from a shortened life expectancy and reduced quality of life compared with the general population. During the natural history period, the average age of death for a male with classic Fabry disease is 50 years old and the average life expectancy for females is reported to be 70 years, a reduction of 10-15 years shorter than the general population.<sup>4-7</sup>

In 2003, agalsidase beta (Fabrazyme<sup>®</sup>) was approved by the FDA as the first treatment available in the US for use in patients with Fabry disease based on clinical trial data showing Fabrazyme reduces globotriaosylceramide (GL3) deposition in capillary endothelium of the kidney and certain other cell types. Fabrazyme is a recombinant form of human  $\alpha$ -galactosidase A and is indicated for use in all patients with Fabry disease, regardless of age or underlying genotype.<sup>8</sup>

In the largest placebo-controlled clinical trial program completed in Fabry disease to-date, Fabrazyme demonstrated clearance of GL-3 from the microvascular endothelium of the kidney, heart and skin cells to normal or near normal levels compared to placebo. In patients with advanced Fabry disease, when adjusted for baseline proteinuria, treatment with Fabrazyme 1.0mg/kg/EOW demonstrated reduced risk of Fabry-related cardiac, renal and cerebrovascular events or death by 61% compared with placebo.<sup>10</sup>

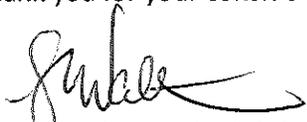
An analysis of 1,044 adult patients who were enrolled in the Fabry disease registry and treated with Fabrazyme for at least 5 years found the incidence rate for severe clinical events, which included renal failure, cardiac events, stroke, and death, decreased from 111 events per 1,000 patient years in the first 6 months of treatment to a range of 40 to 58 events per 1,000 patient years for the remainder of the treatment follow-up period.<sup>11</sup>

After a median of 10 years, data collected from patients in the original Ph III trial who were treated with Fabrazyme 1.0mg/kg/EOW, revealed that 94% (49/52) of patients were still alive and 81% (42/52) remained free of severe Fabry-related clinical events.<sup>12</sup>

Approximately 74% of all patients develop IgG antibodies to Fabrazyme; most do so within the first 3 months of therapy. In clinical trials and post-marketing safety experience, approximately 1% of patients developed anaphylactic or severe allergic reactions during Fabrazyme infusions. The most common adverse reactions reported with Fabrazyme are infusion associated reactions, which occurred in 59% of patients treated with Fabrazyme during the clinical trials, some of which were severe.<sup>8</sup> Fabrazyme has a similar safety profile in both pediatric and adult patients.<sup>13</sup> Please see the Fabrazyme USPI, which is available at [www.Fabrazyme.com](http://www.Fabrazyme.com).

In conclusion, based on the data presented above and to allow for appropriate management for individual Fabry patients, we request that Medicaid in the state of Oregon allow open access for commercially available treatments in the Fabry class, including Fabrazyme.

Thank you for your consideration.



Angela Walter, M.S., C.G.C.  
Senior Medical Science Liaison  
Field Science Director  
Sanofi US Medical



Kevin Ho, MD  
US Medical Director  
Rare Genetic Diseases  
Sanofi US Medical

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September 26, 2019

Roger A. Citron, RPh  
Drug Use Research & Management Program  
Oregon State University, 500 Summer Street NE, E35  
Salem, Oregon 97301-1079

**RE: Oregon Drug Use Review: Fabry Disease Class Review**

Dear Mr. Citron:

Sanofi is pleased to provide comments to the State of Oregon relative to its upcoming scheduled review of Fabrazyme and, at a broader level, the accessibility of covered outpatient drugs under the Medicaid Drug Rebate Program (MDRP) and Oregon Medicaid. We appreciate the state's continuing efforts to evolve its value assessment and drug evaluation methodologies and to engage with increasingly diverse stakeholders as the movement of the scientific and medical communities continues to embrace innovative products in increasingly rare, serious and life-threatening conditions, and it is in this spirit that we provide our comments on these topics as well.

Sanofi is concerned about the access issues that patients are facing for Fabrazyme – namely, that even though Fabrazyme is required to be available under Oregon Medicaid, patients are often still denied coverage for the product. One of the issues that have been raised is a potential concern regarding the fulfillment of postmarketing commitments for Fabrazyme. However, due to the inherent statistical constraints of pursuing clinical and scientific questions in ultra-rare disease populations through the use of randomized controlled trials (RCT), the entirety of Sanofi's postmarketing commitments for Fabrazyme, as agreed upon with FDA and outlined in their public-facing database<sup>1</sup>, will be based on real-world evidence (RWE) from the Fabry Registry. Aside from the foregoing, FDA has already addressed the necessary questions about the safety and efficacy of Fabrazyme, by granting its approval of the product under an accelerated approval pathway. Further, CMS has made its position clear that covered outpatient drugs approved under an "accelerated approval" pathway must be covered by state Medicaid programs<sup>2</sup>. State actions narrowing coverage past the benchmarks outlined by the federal government in subpart h, and reiterated in the attached CMS Medicaid Drug Rebate Program Notice 185, thwarts both the intent of Congress and those executive agencies in establishing access to significant medications for life-threatening diseases. Further, if the basis for Oregon's failure to consistently cover Fabrazyme under its Medicaid program is a concern regarding safety, we note that there are already federal mechanisms in place aimed at removing accelerated approval products which fail to meet the ongoing efficacy and safety requirements required by the FDA per Sec. 21CFR314.530. If the FDA subsequently withdraws

its approval, the drug would no longer meet the definition of a covered outpatient drug and would not be covered under the MDRP. Oregon's inconsistent coverage of Fabrazyme constitutes a de facto challenge to the federal mandate that certain FDA-approved medicines must be covered under the federal Medicaid program. Oregon should not be permitted to implement restrictions to coverage which exceed the limitations already determined by the federal government.

Decision making in health care is inherently complex as numerous objectives need to be balanced. The diverse U.S. healthcare system requires the use of sophisticated methods and processes to provide the best guidance to decision-makers, which must be based on the assessment of the best possible scientific evidence and the holistic understanding of the value of therapies.

We thank the state of Oregon for soliciting input on this review and hope that our recommendations will be considered and integrated into the final decision. We are pleased to engage in additional discussion on these issues or otherwise assist at any time.

Sincerely,



Deanne Calvert  
Head of Sanofi State Government Affairs

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**Center for Medicaid and CHIP Services**

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**June 27, 2018**

**MEDICAID DRUG REBATE PROGRAM NOTICE**

**Release No. 185**

## **For State Technical Contacts**

### **State Medicaid Coverage of Drugs Approved by the FDA under Accelerated Approval Pathway**

This release specifies that a drug approved by the Food and Drug Administration (FDA) under its “accelerated approval” pathway, which is the approval program authorized under section 506(c) of the Federal Food, Drug, and Cosmetic Act (FFDCA), (<https://www.fda.gov/ForPatients/Approvals/Fast/ucm405447.htm>), must be covered by state Medicaid programs, if the drug meets the definition of “covered outpatient drug” as found in Section 1927 of the Social Security Act (the Act).

Section 1927(k)(2)(A)(i) the Act defines a covered outpatient drug, to include a drug “...which is approved for safety and effectiveness as a prescription drug under section 505 or 507 of the [FFDCA]....” Since section 506(c)(1)(A) of the FFDCA provides that an accelerated approval for a drug product is an approval under section 505(c) of the FFDCA, such a drug meets the definition of covered outpatient drug, under section 1927(k)(2) of the Act when used for a medically accepted indication as defined in section 1927(k)(6) of the Act. Section 506(e)(2) of the FFDCA further provides that section does not alter the standards of evidence required under section 505(c) for approval, including the standards regarding whether a product is safe and effective. We note that the FDA accelerated approval process also applies to products licensed under section 351(a) of the Public Health Service Act, which are generally biological products, including vaccines. Such biologicals would also fall under the definition of covered outpatient drug at section 1927(k)(2)(B) of the Act. However, we note that as indicated in section 1927(k)(2)(B), vaccines do not fall under the definition of covered outpatient drug under section 1927(k) of the Act.

Therefore, as with any other drug, if the drug is labeled by a manufacturer that has signed a Medicaid National Drug Rebate Agreement, and the drug meets the definition of covered outpatient drug, then the drug is covered by the Medicaid Drug Rebate Program (MDRP) and is to be covered by state Medicaid programs. If the FDA subsequently withdraws its approval, the drug would no longer meet the definition of a covered outpatient drug and would not be covered under the MDRP. Also, section 1927(k)(6) of the Act defines medically accepted indication, in part, to mean “any use for a covered outpatient drug which is approved under the Federal Food, Drug, and Cosmetic Act,” and section 1927(k)(3) of the Act specifically limits the definition of covered outpatient drug to exclude when a drug is “used for a medical indication which is not a medically accepted indication.”

In summary, this release clarifies that drugs that are granted “accelerated approval” are drugs approved by FDA under section 505(c) of the FDCA, and are able to satisfy the definition of covered outpatient drug, and if used for a medically-accepted indication, then the drug must be covered by state Medicaid programs if the manufacturer has an applicable signed Medicaid national drug rebate agreement for participation in the MDRP. States can use utilization management mechanisms such as prior authorization to assure appropriate use of these medications.

### **Background on FDA’s Accelerated Approval Program**

Section 506(c) of the FDCA allows the FDA to grant accelerated approval to a drug for a serious or life-threatening disease or condition. Part of the criteria for accelerated approval under section 506(c) is a demonstrated effect on either:

- a. A surrogate endpoint that is reasonably likely to predict a clinical benefit, taking into account severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments, or
- b. A clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.

Drugs granted accelerated approval by FDA under the process described in 506(c) of the FDCA are approved under section 505(c) of the FDCA and must meet the same statutory evidentiary standards for safety and effectiveness as those granted traditional approvals. See section 506(e)(2) of the FDCA. Thus, as noted above, at the time a product is granted accelerated approval, FDA has based such an approval on a determination that the drug has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint other than survival or irreversible morbidity.<sup>1</sup>

If you have any questions regarding this topic, please contact [RxDrugPolicy@cms.hhs.gov](mailto:RxDrugPolicy@cms.hhs.gov).

Sincerely,

/s/

Michael Nardone  
Director  
Disabled and Elderly Health Programs Group

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<sup>1</sup> See sections 505(a), 505(c), 506(c), and 506(e)(2) of the FDCA; see also 21 CFR 314.510