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RESEARCH REPORT

Recommendations on Reintroduction of Agalsidase Beta for Patients with Fabry Disease in Europe, Following a Period of Shortage

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Abstract The interruption of the manufacturing process of agalsidase beta has led to a worldwide shortage of this drug. In the EU, nearly all patients initially reduced their agalsidase beta dose, and many of these switched to agalsidase alfa (Replagal Shire HGT). The clinical consequences of this period of drug shortage need to be further evaluated. A gradual

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increase of agalsidase beta supply is now expected. This implies that patients could resume or even commence agalsidase beta treatment. Guidance for prioritization of patients is needed to support equitable distribution of agalsidase beta to EU member states. To achieve this, in absence of level I clinical evidence, a draft consensus proposal was initiated and distributed. No full consensus was achieved, as there is disagreement regarding the indications for switching patients from agalsidase alfa to agalsidase beta. Some physicians support the concept that the 1.0 mg/kg EOW dose of agalsidase beta is more effective than agalsidase alfa at 0.2 mg/kg EOW, while others believe that at recommended dose, the preparations are equivalent. In light of these difficulties and the uncertainties with respect to supply of agalsidase beta, recommendations were agreed upon by a subgroup of physicians. These current recommendations focus on prioritization of criteria indicative of disease progression.

Background

A viral contamination of Genzyme Corporation's production facility in June 2009 and subsequent ongoing manufacturing problems have caused an acute and prolonged shortage of agalsidase beta (Fabrazyme®) to approximately 30 % of prior global supply (Linthorst et al. 2011). This agalsidase beta shortage has resulted in anxiety among patients and those caring for Fabry patients, and its effects need to be studied thoroughly. In Europe and some other parts of the world, alternative treatment with another alpha galactosidase A preparation (agalsidase alfa, Replagal™ Shire Human Genetic Therapies, Inc.) is available and most patients in the EU subsequently switched to agalsidase alfa 0.2 mg/kg/EOW. The European Medicines Agency (EMA) reported a trend of increasing reports of adverse events during the shortage (EMA report dated 19 November 2011), which decreased following switch to agalsidase alfa or reinstitution of the full dose (1.0 mg/kg) of agalsidase beta. A subgroup seemed to have no obvious clinical deterioration due to the lowered dose. In a small study, clinical significant changes at lower dose could not be objectified, but biochemical analysis pointed towards recurrence of storage after switch to low-dose agalsidase beta and subsequent switch to agalsidase alfa (Smid et al. 2011), while another study reported increase in subjective symptoms (Australian State Fabry Disease Treatment Centers et al. 2011). These data are in line with earlier reports showing evidence of deterioration in a subset of patients after switching from agalsidase beta 1.0–0.3 mg/kg. (Lubanda et al. 2009) The EMA recommended monitoring patients closely when on lower than recommended dose of agalsidase beta and change to full dose or to agalsidase alfa in case of deterioration (EMA report 19 November 2011).

In the USA, only agalsidase beta is commercially available and patients have had prolonged treatment interruptions and/or received lower dosages of agalsidase beta than the recommended 1.0 mg/kg/EOW. Some patients also received agalsidase alfa on a compassionate basis or within research protocols.

The possibility to switch to agalsidase alfa as an alternative treatment resulted in unprecedented demand of agalsidase alfa and this led to fears of a shortage of agalsidase alfa in the last quarter of 2010. Although this never actually occurred, in 2010 recommendations on prioritization of enzyme replacement therapy (ERT) for naïve patients were agreed by a group of Fabry experts and

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patient representatives and these have subsequently been published (Linthorst et al. 2011). These recommendations emphasized that patients who had reversible disease manifestations should receive priority over those patients who may have more severe disease, but less reversible. We endorse this principle with respect to those patients who are already on treatment and for whom a change in ERT preparation is considered.

The manufacturer of agalsidase beta (Genzyme-Sanofi) has taken steps to secure future agalsidase beta production, and it is anticipated that in 2012, availability of agalsidase beta will gradually increase. These recommendations address how this extra agalsidase beta should be distributed within patients and the member states of the EU. An initiative was launched to try to achieve consensus within the group of treating physicians with respect to prioritization of patients. To achieve the broadest discussion, also physicians outside the EU were asked to comment.

Preference of agalsidase beta 1.0 mg/kg/EOW over agalsidase alfa 0.2 mg/kg/EOW (or vice versa) is not based on level I clinical evidence. Both preparations have shown clinical efficacy in patients, but it is also known that despite treatment with agalsidase beta or agalsidase alfa at the respective recommended doses, progression of disease occurs in a subset of patients. For instance, those with extensive cardiac fibrosis (Weidemann et al. 2009) or those with low estimated glomerular filtration rate (eGFR) or manifest proteinuria (Germain et al. 2007; Schiffmann 2005) at the initiation of ERT demonstrate ongoing progression of disease when compared to those without (severe) cardiac fibrosis or with preserved eGFR.

These recommendations are indicated only for the period of reduced agalsidase beta availability.

Methods

A draft proposal was written and subsequently distributed by email to treating physicians and patient organizations (represented by the board members of the Fabry International Network). All were asked for their opinions. Following review of these responses, the consensus document was finalized and agreed.

In these recommendations, dosages refer to the Summary of Product characteristics (SmPC) of agalsidase alfa (0.2 mg/kg) (Summary of Product Characteristics Replagal [Internet]. [cited 2012]) and agalsidase beta (1.0 mg/kg) (Summary of Product Characteristics Fabrazyme [Internet]. [cited 2012]). For agalsidase beta, based on the previously mentioned study, the SmPC states that while no definitive conclusion regarding the dose maintenance regimen can be drawn, the findings suggest that, after an initial debulking dose of 1.0 mg/kg every 2 weeks, 0.3 mg/kg every 2 weeks may be sufficient in some patients to maintain clearance of GL-3. Since the number of patients was small and long-term outcome is unknown, 0.3 mg/kg is not recommended. Thus, for clarity, in the following text, a licensed recommended dose means 0.2 mg/kg agalsidase alfa EOW and 1.0 mg/kg agalsidase beta EOW.

Results and Discussion

The initial draft was sent to 47 physicians, of whom 28 provided comments. With regard to the final recommendations, 26 were supportive, 1 could not support the recommendations, and the remainder ($N = 20$) did not respond ($N = 16$) or declined to participate in the discussion ($N = 4$). Those supportive are listed as co-authors. Some physicians indicated during the discussions that a formal prioritization was not feasible. This may relate to the many uncertainties both with respect to availability as well as to the usefulness of prioritization. Some physicians, outside of the EU, felt that they should not be part of this discussion. From others, mixed reactions were received indicating that a true consensus could not be achieved. The main disagreements were criteria for prioritization, uncertainty regarding whether some of these criteria were actually reversible by switching to another enzyme preparation and a desire to make individual decisions rather than having to adhere to recommendations. These recommendations are meant to provide the best possible advice for clinicians to use as guidance relating to the reintroduction of agalsidase beta.

ERT Current Situation

Following the release of the previous consensus document on prioritization of ERT-naïve patients in December 2010, and in accordance with EMA recommendations (EMA 22/Oct/2010), patients in the EU are primarily treated with 1.0 mg/kg/EOW agalsidase beta or with agalsidase alfa 0.2 mg/kg/EOW; only few cases are treated with agalsidase beta $<$ 1.0 mg/kg/EOW. Currently, extra agalsidase beta is expected to become available for an additional 100 patients in Q2 of 2012, and it is expected that in Q3 and Q4 quarter of 2012, availability will further increase. However, uncertainty remains regarding the level of the increase and the delay before all limitations on agalsidase beta will be lifted. Governmental financial issues (involuntary dose reduction) or physician/patient preference (voluntary choice) means that some patients are treated with a dosage of agalsidase beta $<$ 1.0 mg/kg (i.e. not the recommended dose), despite previous recommendations (Linthorst et al. 2011). To the best knowledge of the experts, this is limited to less than 15 cases in the EU. If a patient is treated with a lower than recommended dose, this should be done so in full

agreement between patient and physician, while maintaining close monitoring of therapeutic outcome. In those few patients where treatment with a lower dose of agalsidase beta is voluntary, signs of disease progression should be followed by a switch to agalsidase alfa or beta at recommended dose. It should be noted that while these recommendations are focused on the temporary shortage of agalsidase beta, there is abundant agalsidase alfa available for treatment.

Basic Principles of Treatment

1. Patients with Fabry disease can develop additional complications despite optimal treatment, while receiving comprehensive supportive therapy and ERT at licensed recommended dose.
2. There is currently no level 1 scientific evidence showing superiority of one enzyme preparation over the other (Vedder et al. 2007; Sirrs et al. 2010).
3. Patients should be treated with licensed recommended doses of agalsidase alfa and agalsidase beta.

Criteria for Prioritization

These criteria are based on the current severity of the disease, its rate of progression and the potential for reversibility of disease with ERT and not on age or gender (see also Table 1). Thus, the criteria apply for both the adult and paediatric population for male and female Fabry patients. These criteria only apply during the period of increased yet limited supply of agalsidase beta.

1. A switch to agalsidase beta 1.0 mg/kg/EOW should only be considered if there is a reasonable chance that this dose can be maintained. It is recommended that Genzyme-Sanofi build up a significant stock reserve to accommodate fluctuations in agalsidase beta production. A stock reserve of 3 months of treatment per patient is the minimum requirement for a patient to be able to switch.
2. Patients should be treated for at least 12 months with agalsidase alfa 0.2 mg/kg/EOW, before a switch to agalsidase beta 1.0 mg/kg /EOW can be considered.
3. A dose increase may especially be relevant in patients with anti-agalsidase antibodies. In these patients, a more robust reduction of (lyso)ceramide trihexoside (CTH) after dose increase is seen in plasma or urine as shown by various groups (Linthorst et al. 2004; Whitfield et al. 2005; Ohashi et al. 2007; Vedder et al. 2008; Van Breemen et al. 2011). However, it has not been documented to date that this additional reduction results in a more favourable clinical outcome. It is advised to screen for anti-agalsidase antibodies in males on ERT (irrespective of treatment or dose).
4. Patients should only be prioritized to switch to agalsidase beta 1.0 mg/kg/EOW treatment if they are demonstrating disease progression on agalsidase alfa 0,2 mg/kg, while there is still potential reversibility of affected organs, and the switch should be undertaken only after full discussion between the patient and physician.
5. Appropriate concomitant and adjuvant therapy (e.g. ACE-inhibitors or angiotensin receptor blockers, pain management, anti-arrhythmic drugs and devices, stroke prophylaxis) must always be considered for all patients (Summary of Product Characteristics Fabrazyme [Internet]. [cited 2012]; Summary of Product Characteristics Replagal [Internet]. [cited 2012]).

The following four steps are anticipated in the process of increase in agalsidase beta availability.

Step I: (Limited Increase in Agalsidase Beta)

All patients in step I include those receiving agalsidase beta <1.0 mg/kg/EOW on an involuntary basis, because of shortage of agalsidase beta (see Basic Principles of Treatment), regardless of whether they are deteriorating or stable. It is perceived that this group is very small. Patients on a lower dose of agalsidase beta can also switch to agalsidase alfa 0.2 mg/kg/EOW.

Step II (Additional Increase in Agalsidase Beta Supply)

All patients in step I have had the opportunity to be treated with recommended dose of agalsidase beta (1.0 mg/kg/EOW)

The following patients now qualify: patients treated with agalsidase alfa 0.2 mg/kg for at least 12 months who demonstrate signs of deterioration and where the physician, after full discussion with the patient, deems a switch to agalsidase beta necessary. Deterioration is defined as having occurred from start of ERT (does not need to have occurred during the agalsidase beta shortage):

(a) Severe neuropathic pains that cannot be satisfactorily controlled despite 3 months of maximum analgesic treatment, in agreement with neuropathic pain management protocols.
(b) Increase in left ventricular mass (at least 10 % on MRI or 20 % by ultrasound) despite treatment, while adult patients may have no or only mild cardiac fibrosis on MRI (fibrosis in only one left ventricle segment) (Weidemann et al. 2009).
(c) A 33 % increase in serum creatinin levels, or a significant decrease in renal function evidenced by means of measured GFR demonstrating progression from CKD I to CKD 2, but only while eGFR is above 30 ml/min.

Table 1 Priority stages for previously untreated Fabry patients (Taken from Linthorst et al. (2011))

Priority stage	Characteristics
High priority – children	Severe neuropathic pain unresponsive to a maximum trial of 3 months of optimal pain management (Filling-Katz et al. 1989; Weidemann et al. 2010)
	Persistent microalbuminuria defined by the median of three consecutive early morning urine samples
	24 h urinary protein >250 mg/day at presentation (consider simultaneous use of ACE inhibitors)
	In females, if microalbuminuria or proteinuria is the only clinical manifestation, a trial of ACE inhibitors for a period of 3–6 months in the first instance is recommended
	Age-adjusted left ventricular mass index ≥ 90th percentile
	TIA/stroke and/or MRI brain showing white matter lesions (subclinical or with clinical manifestations)
High priority – adults	Disease age of onset < 50 years
	Increased LVM without MRI evidence of extensive fibrosis
	GFR between 30 and 90 ml/min/1.73 m (Smid et al. 2011)
	Urine protein 0.3–1.0 g/24 ho[a]
	Severe neuropathic pain, if persistent after optimal pain management (Filling-Katz et al. 1989; Weidemann et al. 2010)
	Cerebrovascular disease
Intermediate priority	Less reversible disease
	Increased LVM with fibrosis
	GFR < 30 ml/min/1.73 m (Smid et al. 2011)
	Less severe disease:
	Disease age of onset > 50 years[b]
Low priority	End-stage cardiac disease (Weidemann et al. 2011)
	End-stage CNS disease, e.g. multi infarct dementia
	Multiple organ failure
	Life expectancy of less than 1 year due to other co-morbidities
	Those patients mildly affected (e.g. without LVH, acroparesthesias well controlled with optimal pain medication, eGFR > 90 ml/min/1.73 m (Smid et al. 2011))

[a] At presentation, with or without ACE inhibitors or angiotensin II receptor blockers

[b] Age of onset is the perceived age at which symptoms occurred which can be attributed to Fabry disease

- In case of serial serum creatinin measurements, at least 12 months of treatment should have been employed and two consecutive creatinin values at least 1 week apart should document a persistent increase in creatinin.
- After other causes of renal deterioration have been excluded,

(d) New (clinical) stroke/transient ischaemic attack (TIA) as documented by a neurologist not thought to be related to aging or other co-morbidities.

(e) Hospitalization due to cardiac disease (e.g. cardiac failure, rhythm disturbances, or additional interventions to treat these (such as pacemaker or Implantable Cardioverter-Defibrillator (ICD), CABG, valve surgery).

Step III (Further Increase in Availability)

All patients in step II for whom the physician/patient deems a switch necessary and have agreed to do so, have been switched. Now, the following patients can be considered for switch (again after full discussion between the patient and the treating physician):

(a) Patients currently treated with agalsidase alfa 0,2 mg/kg, where the physician/patient deems a switch to agalsidase beta necessary, but the patient is deteriorating (see above), but has an eGFR<30, is on dialysis, had a renal transplant or severe cardiac fibrosis (two or more left ventricle segments).

(b) Currently untreated patients belonging to the high priority of ERT naïve patients, as mentioned in the previous recommendations (see Table 1), for whom the treating physician has a preference of agalsidase beta 1.0 mg/kg over agalsidase alfa 0.2 mg/kg.

Step IV (Unlimited Supply of Agalsidase Beta)

No restrictions apply. Evaluate the possible benefits of switching back to agalsidase beta on an individual patient basis. We would advise that patients who are being treated

with doses other than the licensed recommended doses should be monitored with particular care.

There is no level 1 evidence comparing the effectiveness of agalsidase alfa and agalsidase beta at their recommended doses. We have stated above that patients receiving agalsidase alfa 0.2 mg/kg EOW for more than 1 year and are deteriorating could be considered for switch to agalsidase beta 1.0 mg/kg/day. While these recommendations focus on the agalsidase beta shortage and not on switching patients to other preparations in general, patients on agalsidase beta 1.0 mg/kg/EOW for a year and deteriorating could be considered for switch to agalsidase alfa 0.2 mg/kg EOW.

Genzyme Corporation-Sanofi, the manufacturer of agalsidase beta is willing to allocate increase in agalsidase beta supplies in accordance to these recommendations. However, this can only occur if physicians can provide information on the expected number of patients per country/region/treatment centre for whom they prefer to switch to agalsidase beta. We advise all treating physicians to remain in close communication with their local Genzyme-Sanofi representative in order to help them with the allocations.

Assessment of Patients and Storage of Samples for Future Biomarkers

There is only limited information on the efficacy on ERT with lower dosages of agalsidase beta or in patients who switched from agalsidase beta to agalsidase alfa (and back). Physicians caring for Fabry patients are strongly encouraged to carefully document changes in the course of the disease when treatment regimens are varied and to perform detailed physical examinations when patients are about to switch treatments. In addition, storage of samples before and after the switch (serum, plasma, urine) is strongly encouraged as these can be used for future analysis of biomarkers and antibodies. The current period of restricted enzyme supply may aid the Fabry community in gaining more understanding in the outcome of the various different treatment regimens confronting patients.

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