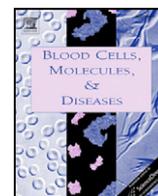




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### Letter to the Editor

#### Guidelines for the restart of imiglucerase in patients with Gaucher disease: Recommendations from the European Working Group on Gaucher disease

To the Editor,

Between July and December 2009, global shortage of imiglucerase for the treatment of Gaucher disease has occurred due to a viral contamination of the manufacturer's (Genzyme) single production facility, which necessitated its temporary shut-down. As a result, only 20% of the prior global supply has been available, leading to either interruption of treatment, dose reduction, or starting of alternative treatments. The European Working Group on Gaucher Disease (EWGGD), supported by the European Gaucher Alliance (EGA), issued guidelines as how to protect the most vulnerable patients and discussed options for alternative treatments. In addition, an emergency program was launched for patients that met criteria for being at risk for the development of complications [1]. With the pending restoration of the full production of imiglucerase from the end of 2009 onwards, Genzyme suggested to the EWGGD to produce recommendations for the re-installation of imiglucerase. An unfortunate concern has risen with respect to contamination of <1% vials of imiglucerase (as well as of additional enzymes produced at the same manufacturer facility) with foreign particles, including stainless steel fragments, non-latex rubber from the vial stopper, and fiber-like material. The FDA has required that a "Dear Healthcare Professional Letter" was issued with recommendations for inspection of the solution and for the use of 0.2- or 0.22- $\mu$ m filters [2].

These recent events raise the following considerations:

1. Can patients resume their previous dose, at an equal infusion rate and at the same site? Are there any specific recommendations following the finding of particles in imiglucerase vials?
2. Can patients continue their alternative treatments?
3. Which disease parameters should be recorded at and after restoring treatment with imiglucerase?

The EWGGD clinicians and researchers and leading members of the EGA were approached by e-mail. Input from 17 members was retrieved to reach the following recommendations:

1. In principle, patients who had an interruption of therapy or were treated with a much lower dose could re-start at their previous dose. Even if there has been a deterioration in either one of these parameters, the previous dose should be probably sufficient for improvement. We recommend not to prescribe higher dosages, unless the disease deteriorated as defined previously [1] despite reinstatement of therapy. This may especially apply to children, who are considered to be more vulnerable. In patients who have remained stable, a prolonged continuation of the lower dose regimen is acceptable. In view of some of the physicians, prolonged treatment interruption may also be an option if patients comply to strict monitoring, keeping restart of enzyme therapy open.

Infusion times should be adjusted to dose. There is no need for those patients previously receiving home therapy to have their resumed infusions in a hospital setting, with the exception of patients with prior moderate to severe infusion-related reactions.

Regarding the recent information of the contamination of vials of imiglucerase by foreign particles, we recommend to implement the FDA guidelines (for careful inspection and for use of filters) to all patients worldwide [2]. Some clinicians feel that the use of the recommended very small endotoxin-retaining 0.2-/0.22- $\mu$ m filters should be sufficient to arrest these larger particles. Others advocate that some patients with less aggressive disease may be able to wait until clean vials become available or until the manufacturers confirm the ability of the 0.2-/0.22- $\mu$ m filters to block the passage of the particles into the bloodstream.

2. Patients that have started on either velaglucerase (GA-GCB, Shire Human Genetic Therapies, MA, USA), taliglucerase (prGCD, Protalix Biotherapeutics, Carmiel, Israel), or substrate reduction therapy (miglustat, Actelion therapeutics) should be able to continue these treatments if they have a satisfactory response and tolerate the treatments well. Miglustat is licensed for the oral treatment of type 1 Gaucher patients with mild and moderate forms of the disease, for whom enzyme replacement therapy is unsuitable. When the supply of imiglucerase return to normal, priority should be given to patients with more severe disease or those that have recurrence of disease activity to switch back to enzyme therapy, followed by patients who do not prefer oral treatment. Velaglucerase and taliglucerase are not yet fully licensed, but several European countries have allowed the use of these enzymes via early access programs. Local regulatory policies, as well as the patients' and physicians' choice, will guide whether or not patients will continue on these new enzymes or switch back to imiglucerase. Both Shire and Protalix have indicated that they are willing to provide enzyme regardless of the timing of reimbursement before or after official approval of the drugs. The EWGGD supports this continued access to both new enzymes, which were found to be safe and effective in the studies conducted so far for registration purposes.
3. In all instances, i.e., restart of previous imiglucerase regimens, dose increase, continuation of low dose, drug vacation, or alternative therapies, we recommend close monitoring of the patients at 3- to 6-month intervals for clinical events, including physical examination, hemoglobin value, platelet count, and measurement of biomarkers, such as chitotriosidase. Organ volumes and MRI of the lumbar spine and/or femurs or DEXA scans should be determined preferably at intervals of 6 or 12 months. For the period of drug interruption or dose reduction, we recommend that a comprehensive analysis is conducted in early 2010 to assess the clinical and biochemical effects of the reduction of imiglucerase supply for Gaucher patients. We would like to support the use of the Gaucher Registry for a large-scale analysis, but in addition, the feasibility to collect data independently through the EWGGD will be discussed.

In conclusion, in the unusual circumstances in which the global supply of imiglucerase has been reduced, the introduction of several alternative agents for the treatment of Gaucher disease has been rapidly expedited. We recommend that imiglucerase should be restored in patients who need it to their previous dose therapy; we also suggest that where applicable, administration of the alternative treatments should continue. Careful clinical monitoring and scrupulous recording of key parameters of Gaucher disease activity should contribute to the evaluation of therapeutic choices within the expanding medicinal arsenal now available for this disorder.

## References

- [1] C.E. Hollak, S. Vom Dahl, J.M. Aerts, et al., Force Majeure: therapeutic measures in response to restricted supply of imiglucerase (Cerezyme) for patients with Gaucher disease, *Blood Cells Mol. Dis.* (2009) (Oct 3 Electronic publication ahead of print).  
 [2] <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm190400.htm>.

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