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Narrative Review

Management and monitoring recommendations for the use of eliglustat in adults with type 1 Gaucher disease in Europe☆

Nadia Belmatoug [a,*], Maja Di Rocco [b], Cristina Fraga [c], Pilar Giraldo [d], Derralynn Hughes [e], Elena Lukina [f], Pierre Maison-Blanche [g], Martin Merkel [h], Claus Niederau [i], Ursula Plöckinger [j], Johan Richter [k], Thomas M. Stulnig [l], Stephan vom Dahl [m], Timothy M. Cox [n]

[a] Referral Center for Lysosomal Diseases, University Beaujon Hospital Paris Nord Val de Seine, Assistance-Publique Hôpitaux de Paris, Department of Internal Medicine, 100 Boulevard du Général Leclerc, 92110 Clichy, France
[b] Unit of Rare Diseases, Department Pediatrics, Gaslini Institute, Largo Gaslini 3, 16147 Genoa, Italy
[c] Department of Haematology, HDES Hospital, Ponta Delgada, Av. D. Manuel I, PDL, Açores, Portugal
[d] Translational Research Unit, Instituto Investigación Sanitaria Aragon, CIBER Enfermedades Raras (CIBERER), Zaragoza, Spain
[e] Royal Free London NHS Foundation Trust, University College London, Department of Haematology, Pond St., London NW1 2QG, United Kingdom
[f] Department of Orphan Diseases, Hematology Research Center, 4 Novy Zykovsky Lane, 125167 Moscow, Russia
[g] Bichat University Hospital, Cardiology Unit, 46 Rue Henri Huchard, 75018 Paris, France
[h] Department of Internal Medicine, Asklepios Klinik St. Georg, Lohmühlenstr. 5, 20099 Hamburg, Germany
[i] Katholisches Klinikum Oberhausen GmbH, St. Josef Hospital, Department of Medicine, Academic Teaching Hospital, Universität Duisburg-Essen, Mülheimer Str. 83, 46045 Oberhausen, Germany
[j] Interdisziplinares Stoffwechsel-Centrum: Diabetes, Endokrinologie und Stoffwechsel, Charité Universitätsmedizin Berlin, Campus Virchow-Klinikum, Augustenburger Platz 1, 13352 Berlin, Germany
[k] Department of Hematology and Vascular Diseases, Skåne University Hospital, 221 85 Lund, Sweden
[l] Clinical Division of Endocrinology and Metabolism, Department of Medicine III, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria
[m] Department of Gastroenterology, Hepatology and Infectious Diseases, University Hospital, University of Duesseldorf, Moorenstrasse 5, D-40225, Germany
[n] Department of Medicine, University of Cambridge, Box 157, Level 5, Addenbrooke's Hospital, Cambridge CB2 0QQ, United Kingdom

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ABSTRACT

Purpose: In Gaucher disease, diminished activity of the lysosomal enzyme, acid β-glucosidase, leads to accumulation of glucosylceramides and related substrates, primarily in the spleen, liver, and bone marrow. Eliglustat is an oral substrate reduction therapy approved in the European Union and the United States as a first-line treatment for adults with type 1 Gaucher disease who have compatible CYP2D6 metabolism phenotypes. A European Advisory Council of experts in Gaucher disease describes the characteristics of eliglustat that are distinct from enzyme augmentation therapy (the standard of care) and miglustat (the other approved substrate reduction therapy) and recommends investigations and monitoring for patients on eliglustat therapy within the context of current recommendations for Gaucher disease management.

Results: Eliglustat is a selective, potent inhibitor of glucosylceramide synthase, the enzyme responsible for biosynthesis of glucosylceramides which accumulate in Gaucher disease. Extensive metabolism of eliglustat by CYP2D6, and, to a lesser extent, CYP3A of the cytochrome P450 pathway, necessitates careful consideration of the patient's CYP2D6 metaboliser status and use of concomitant medications which share metabolism by these pathways. Guidance on specific assessments and monitoring required for eliglustat therapy, including an algorithm to determine eligibility for eliglustat, are provided.

Conclusions: As a first-line therapy for type 1 Gaucher disease, eliglustat offers eligible patients a daily oral therapy alternative to biweekly infusions of enzyme therapy. Physicians will need to carefully assess individual Gaucher patients to determine their appropriateness for eliglustat therapy. The therapeutic response to eliglustat and use of concomitant medications will require long-term monitoring.

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Abbreviations: BMD, bone mineral density; ECG, electrocardiogram; ERT, enzyme replacement therapy; ICGG, International Collaborative Gaucher Group.

☆ Supported by: Sanofi Genzyme.

* Corresponding author at: Referral Center for Lysosomal Diseases, University Beaujon Hospital Paris Nord Val de Seine, Assistance-Publique Hôpitaux de Paris, Department of Internal Medicine, Paris Nord Val de Seine, site Beaujon, 100 Bd du Général Leclerc, 92110 Clichy, France. Tel. +33 140875286; fax: +33 140874434.
E-mail addresses: nadia.belmatoug@aphp.fr (N. Belmatoug), majadirocco@ospedale-gaslini.ge.it (M. Di Rocco), maria.cf.barros@azores.gov.pt (C. Fraga), giraldocastellano@gmail.com (P. Giraldo), elenalukina02@gmail.com (E. Lukina), ipmb@wanadoo.fr (P. Maison-Blanche), m.merkel@asklepios.com (M. Merkel), c.niederau@kk-ob.de (C. Niederau), ursula.ploeckinger@charite.de (U. Plöckinger), johan.richter@med.lu.se (J. Richter), thomas.stulnig@meduniwien.ac.at (T.M. Stulnig), Stephan.vomdahl@med.uni-duesseldorf.de (S. vom Dahl), tmc12@medschl.cam.ac.uk (T.M. Cox).

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1. Introduction

Eliglustat is an oral substrate reduction therapy approved in the European Union (2015) and the United States (2014) as a first-line treatment for adults with type 1 Gaucher disease who are extensive, intermediate, or poor metabolisers, as predicted by genotyping the cytochrome P_{450} CYP2D6 locus [1]. It joins enzyme replacement therapy (ERT) as a first-line therapy for the disease. As an oral therapy, eliglustat also offers advantages over ERT with respect to time spent on therapy; compatibility of treatment with job, family, and social commitments; and, probably, improved quality of life.

Venous infusions of ERT have been in wide use for more than two decades. The therapy is usually well tolerated and considered safe, and infusion at the patient's home is possible in those countries where home infusions are supported by the health care system. ERT is typically prescribed by physicians experienced in treating Gaucher disease. Its prescription requires consideration of the patient's body weight and titration to therapeutic efficacy. As a result of its genetically determined metabolism in the liver, eliglustat requires individual adaptation of the dose and careful supervision of concomitant medications.

In this review, the distinctive characteristics of eliglustat are set out, together with the necessary basic investigations and monitoring required during maintenance of this therapy. All other aspects of the current recommendations for management of Gaucher disease [2–5] remain unchanged. The authors are members of a European Advisory Council consisting of leading experts in Gaucher disease convened by Sanofi Genzyme to consider the appropriate use of eliglustat in the treatment of adults with type 1 Gaucher disease. This position statement reflects the consensus reached by the Council based on the European product label for eliglustat and their collective clinical experience treating patients with Gaucher disease. An independently convened panel of United States (US) experts in Gaucher disease recently published recommendations for use of eliglustat which are consistent with the US product label, including different dosing regimens in the context of clinical practice in the US [6].

2. Current management of Gaucher disease

Gaucher disease is an inherited disease due to mutations in both alleles of the acid β-glucosidase gene resulting in deficient activity of the lysosomal enzyme, acid β-glucosidase [7,8]. The consequent accumulation of its substrates, notably glucosylceramides, primarily in the spleen, liver, and bone marrow can lead to progressive and debilitating manifestations, including spleen and liver enlargement, anaemia, thrombocytopenia, pulmonary disease, immune dysfunction, bone pain, osteoporosis, avascular necrosis (osteonecrosis), osteolytic lesions and destruction of joints [2,3,7–13]. Types 2 and 3 Gaucher disease also affect the central nervous system. Type 1 Gaucher disease, the so-called non-neuronopathic form, is the most common form in the United States and Northwestern European populations, affecting an estimated 1 in 40,000 to 1 in 60,000 individuals [14]; there is a higher prevalence among Ashkenazi Jews [8].

The diagnosis of Gaucher disease is confirmed by demonstrating decreased acid β-glucosidase activity in leukocytes and/or by molecular analysis of the *GBA1* gene to identify two mutations plausibly in *trans* either previously associated with the disease or judged to be disabling for catalytic function or enzyme integrity [2,15]. In the case of inconclusive residual enzyme activity, the presence of two known mutant alleles in the *GBA1* gene is diagnostic [15]. Enzyme therapy with imiglucerase (Cerezyme, Sanofi Genzyme, Cambridge, MA, USA) has, over more than 20 years, proved to very effective in Gaucher disease. Two other ERTs (velaglucerase alpha [VPRIV], Shire Human Genetic Therapies, Lexington, MA, USA, and taliglucerase alfa [ELELYSO], Pfizer Labs, New York, NY, USA) have also been approved and are used widely in clinical practice, although taliglucerase alfa is not approved in Europe. Early treatment with imiglucerase for patients with symptomatic disease has been shown to improve outcomes, including regression or amelioration of organomegaly, reversal of anaemia and thrombocytopenia, amelioration of bone pain and bone crises [16], reversal of osteopenia [10], prevention of avascular necrosis (osteonecrosis) [9], improved bone marrow burden score (at higher doses) [17], and improved quality of life [18]. Despite the success of enzyme therapy in treating Gaucher disease, the treatment has limitations, including disease in the skeleton and lungs, which may be refractory despite long-term treatment [19].

Substrate reduction therapy represents an alternative stratagem for ameliorating the effects of Gaucher disease by rebalancing the rate of synthesis of glucosylceramides with their impaired breakdown. Whereas administration of recombinant human acid β-glucosidase augments the endogenous enzyme activity in the patient to enhance the breakdown of accumulated glucosylceramides in the lysosomal compartment of macrophages, substrate reduction therapy inhibits the enzyme glucosylceramide synthase, thereby slowing the over-production of glucosylceramides relative to their rate of recycling in the lysosomal compartment. The oral substrate reduction therapy miglustat (Zavesca, Actelion Pharmaceuticals, Allschwil, Switzerland) has been available in Europe since approval in 2002; however, due to its low to medium efficacy in Gaucher disease and considerable gastrointestinal and neurologic side effects, it is approved in the European Union only as a second-line therapy for patients unsuitable for ERT. Eliglustat (Cerdelga, Sanofi Genzyme, Cambridge, MA, USA), a potent and selective inhibitor of glucosylceramide synthase, was approved in Europe in 2015 as a first-line therapy for adults with type 1 Gaucher disease who are genotyped for CYP2D6 variants and predicted to be extensive, intermediate, or poor metabolisers (categories which apply to more than 90% of type 1 Gaucher patients). Unlike the iminosugar miglustat, eliglustat is a ceramide analogue that inhibits UDP-glucosylceramide synthase without inhibiting intestinal disaccharidases [20,21], thereby avoiding the frequent gastrointestinal side effects encountered with miglustat [22–24]. Miglustat achieves significant distribution in the brain, but is not effective in neuronopathic Gaucher disease [25] and may cause neurologic side effects in type 1 Gaucher disease [22,24]. This is avoided with eliglustat because the multidrug transporter, Pgp-1, prevents eliglustat accumulation in the brain [20,21,26]. As a small molecule with a widespread tissue distribution, eliglustat may prove to be effective at “sanctuary sites” of disease, for example in bone and lung, which are not accessible to treatment with therapeutic enzyme preparations [19]. Furthermore, oral administration of eliglustat provides an advantage to patients when compared with regular intravenous infusions of enzyme therapy (typically given every 2 weeks).

Thus far, 219 patients with type 1 Gaucher disease have been treated with eliglustat in the completed Phase 2 and 3 clinical trials (Table 1). Administration of eliglustat induced clinically meaningful improvements in platelet counts and haemoglobin concentration, spleen and liver volumes, and bone outcomes in previously untreated patients [27–29], which have been maintained up to 18 months in the Phase 3 ENGAGE trial [30] and 4 years in the Phase 2 trial [31]. In patients whose disease had been stabilised with ERT before switching to eliglustat, improved haematological, visceral and bone parameters remained stable after 12 months on eliglustat [32], with improvements maintained up to 2 years [33]. Among 18 patients on eliglustat for 18 months in the ENGAGE trial, mean BMD T-score of the lumbar spine increased from baseline by 0.19 and mean BMD Z-score increased by 0.26 [30]. The 15 patients receiving 4 years of eliglustat therapy in the Phase 2 trial had increases from baseline of 0.7 in both T-score and Z-score of lumbar spine [34]. Longer-term data are needed to fully evaluate eliglustat's effects on bone disease.

3. Eliglustat dosing and drug interactions

Eliglustat is metabolised by enzymes of the cytochrome P450 pathway, preferentially CYP2D6, and, to a lesser extent, CYP3A. Recommendations for eliglustat dosing based on predicted CYP2D6 metaboliser

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