



## Narrative Review

## Management and monitoring recommendations for the use of eliglustat in adults with type 1 Gaucher disease in Europe<sup>☆</sup>



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## ABSTRACT

**Purpose:** In Gaucher disease, diminished activity of the lysosomal enzyme, acid  $\beta$ -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.

<sup>☆</sup> Supported by: Sanofi Genzyme.

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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<sub>450</sub> 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  $\beta$ -glucosidase gene resulting in deficient activity of the lysosomal enzyme, acid  $\beta$ -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  $\beta$ -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  $\beta$ -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

**Table 1**  
Clinical trials of eliglustat.

	Treatment-naïve patients			Patients switching from ERT	
	Phase 2 [27]	Phase 3 [29]		Phase 3 [32]	
	Eliglustat (N = 26)	Eliglustat (N = 20)	Placebo (N = 20)	Eliglustat (N = 106)	Imiglucerase (N = 53)
Primary endpoint	Improvement from baseline to 12 months in ≥2 of 3 main efficacy parameters (spleen volume, haemoglobin level, and platelet count) <sup>a</sup>	Mean percentage change in spleen volume by MRI from baseline to 9 months		Percentage of patients whose haematological parameters and organ volumes remained stable after 12 months <sup>b</sup>	
Primary endpoint met	Yes	Yes		Yes <sup>c</sup>	
Components of primary endpoint	91% (20/22) of completers	Treatment difference: –30%		Stable: 85%	
	12-month change from baseline:	9-month change from baseline:		Stable after 12 months:	
Spleen volume	–38.5%	–27.8%	+2.3%	96%	100%
Liver volume	–17.0%	–5.2%	+1.4%	96%	94%
Haemoglobin	+1.62 mg/dL	+0.69 g/dL	–0.54 g/dL	95%	100%
Platelet count	+40.3%	+32.0%	–9.1%	93%	100%
Bone marrow burden score	Not assessed	Baseline: 10.9	Baseline: 9.8	Baseline: 8.25	Baseline: 8.28
		9 months: 9.8 <sup>d</sup>	9 months: 9.8	12 months: 8.10	12 months: 8.06
Long-term follow-up	48-month change from baseline [31]	18-month change from baseline [30]	9-month change after switch to eliglustat <sup>e</sup> [30]	Stable at 24 months (n = 99) [33]	Stable at 12 months after switch to eliglustat <sup>e</sup> (n = 47) [33]
Spleen volume	–63%	–45%	–31%	96%	97%
Liver volume	–28%	–11%	–7.3%	96%	95%
Haemoglobin	+2.3 g/dL	+1.02 g/dL	+0.79 g/dL	97%	100%
Platelet count	+95%	+58%	+40%	94%	90%
Bone marrow burden score	Not assessed	–2.15	–0.94	Not reported	Not reported

<sup>a</sup> Improvements defined as: a reduction of at least 15% in spleen volume and increases of at least 0.5 g/dL in haemoglobin level and 15% in platelet count.

<sup>b</sup> Stability defined as: haemoglobin concentration that did not decrease more than 1.5 g/dL, platelet count that did not decrease more than 25%, spleen volume in multiples of normal size (MN) that did not increase more than 25%, and liver volume (MN) that did not increase more than 20% from baseline.

<sup>c</sup> In noninferiority analysis, the between groups difference was –8.8% (95% CI: –17.6, 4.2). The lower bound of the 95% CI for the difference in percentage (–17.6%) was within the pre-specified threshold of –25%.

<sup>d</sup> Decrease of 1.1 for eliglustat relative to placebo (P = 0.002).

<sup>e</sup> After the 9-month primary analysis period in ENGAGE, all patients received eliglustat during the extension period. After the 12-month primary analysis period in ENCORE, all patients received eliglustat during the extension period.

status and use of concomitant medications also metabolised by CYP2D6 and CYP3A are shown in Table 2. In brief, the recommended dose of 84 mg eliglustat twice daily for extensive and intermediate metabolisers is reduced to 84 mg once daily in poor metabolisers. (Note that each eliglustat capsule contains 100 mg eliglustat tartrate, which is equivalent to 84 mg of eliglustat.)

Table 2 gives an overview of possible drug–drug interactions and their effects on eliglustat dosing to avoid potential side effects arising from these interactions. Eliglustat is contraindicated for extensive or intermediate metabolisers taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor and for poor metabolisers taking a strong CYP3A inhibitor. Under these conditions, the two main pathways for eliglustat metabolism are impaired and thus substantially elevated eliglustat plasma concentrations would be expected. Concomitant use of eliglustat with strong CYP3A inducers is not recommended, as this substantially decreases exposure to eliglustat, which may reduce its therapeutic efficacy.

In the case of short-term use of additional medication (e.g. a 10-day course of erythromycin), temporary cessation of eliglustat is advised but it can be restarted when the concomitant drug regimen has been completed. As shown in Table 3, there is also potential for drug interaction when eliglustat is taken with medications that are substrates of P-glycoprotein (P-gp) or CYP2D6, as this could result in an increased concentration of the concomitant drug. In this situation, the options are either (i) monitoring the concentration of the concomitant P-gp or CYP2D6 substrate, or (ii) reducing the dose of that drug and/or titration according to its therapeutic efficacy.

As concomitant medications are often prescribed by general or other physicians who share responsibility for other health matters in the patient with Gaucher disease, it is essential that patients and each of their physicians (and any other prescribing health professionals) are informed about the potential for interactions between eliglustat and other medications that affect CYP2D6 and CYP3A metabolism.

Patients need to be informed about the correct mode of administration of eliglustat. The capsules should be swallowed whole, preferably with water; they should not be crushed, dissolved, or opened. If a dose of eliglustat is missed, the next prescribed dose should be taken as scheduled, without any change (i.e. the missed dose being simply omitted). Eliglustat may be taken with or without food since absorption is unaffected. However, grapefruit and grapefruit juice should be avoided, as contain components that inhibit CYP3A with the potential to increase plasma concentrations of eliglustat. Other fruits known to inhibit CYP3A-mediated drug metabolism include pomegranate, carambola (star fruit), and bitter orange (Seville orange) [35–37]. Licorice (*Glycyrrhiza glabra*) contains principles that inhibit CYP3A4 in animal and in vitro studies [38–40]. Although interactions between licorice components and eliglustat have not been studied, as a precautionary measure, it is prudent to avoid consumption of medicinal extracts, confectionary or other preparations of this plant while taking eliglustat.

#### 4. Initial assessments for patients taking eliglustat

Recommendations for assessment and monitoring of patients with type 1 Gaucher disease were first developed by the International Collaborative Gaucher Group (ICGG) in 1998 [2]; in 2004, revised recommendations [4] and therapeutic goals for Gaucher patients [3] were published. These recommendations and therapeutic goals continue to evolve and are subject to revision. Together, the expert guidance provides a general basis of care for Gaucher patients regardless of the type of therapy. It is recommended that patients be thoroughly evaluated at the start of any treatment and regularly thereafter. The nature of the assessments, particularly the radiological ones, will, to a certain extent, be dependent on local resources and their availability, which vary from country to country. Evaluation and management of Gaucher disease should be initiated and supervised by a physician knowledgeable about Gaucher disease. It is generally recommended that patients

**Table 2**  
Eliglustat dosing with concomitant use of CYP2D6 and/or CYP3A inhibitors and inducers based on predicted CYP2D6 metaboliser status (tabulated version of SmPC guidance).

Potential interacting substances		Extensive or intermediate metabolisers		Poor metabolisers		
CYP450 inhibitors		Examples (list is not exhaustive)	Effect on eliglustat exposure	Recommendation	Effect on eliglustat exposure	Recommendation
CYP2D6 inhibitors	Strong CYP2D6 inhibitor	Paroxetine, fluoxetine, bupropion, quinidine	$C_{max}$ : 7.3-fold ↑ AUC <sub>0-12</sub> : 8.9-fold ↑ (eliglustat 84 mg twice daily + paroxetine 30 mg once daily)	Consider eliglustat 84 mg once daily	No data	Standard dose* (84 mg once daily)
	Moderate CYP2D6 inhibitor	Duloxetine, terbinafine, moclobemide, mirabegron, cinacalcet, dronedarone	Predicted up to 4-fold ↑	Caution	No data	Standard dose* (84 mg once daily)
CYP3A inhibitors	Strong CYP3A inhibitor	Clarithromycin, telithromycin ketoconazole, itraconazole, posaconazole, voriconazole, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, boceprevir, conivaptan, cobicistat	$C_{max}$ : 3.8-fold ↑ AUC <sub>0-12</sub> : 4.3-fold ↑ (eliglustat 84 mg twice daily + ketoconazole 400 mg once daily)	Caution	Predicted: $C_{max}$ : 4.3-fold ↑ AUC <sub>0-24</sub> : 6.2 fold ↑	Contraindicated
	Moderate CYP3A inhibitor	Erythromycin, ciprofloxacin, fluconazole, diltiazem, verapamil, aprepitant, atazanavir, darunavir, fosamprenavir, imatinib, cimetidine	Predicted up to 3-fold ↑	Caution	Predicted: $C_{max}$ : 2.4-fold ↑ AUC <sub>0-24</sub> : 3-fold ↑	Not recommended
	Weak CYP3A inhibitors	Amlodipine, cilostazol, fluvoxamine, goldenseal, isoniazid, ranitidine, ranolazine	No data	Standard dose (84 mg twice daily)	No data	Caution
		Grapefruit products	Can increase levels	Avoid	Can increase levels	Avoid
CYP2D6 + CYP3A inhibitors	Strong or moderate CYP2D6 inhibitor PLUS Strong or moderate CYP3A inhibitor	See above	Predicted: $C_{max}$ : up to 17-fold ↑ AUC <sub>0-12</sub> : up to 25-fold ↑	Contraindicated	No data	See above for strong or moderate CYP3A inhibitors in poor metabolisers
CYP3A inducers	Strong CYP3A inducer	Rifampicin, rifabutin carbamazepine, phenobarbital, phenytoin, St. John's wort	85% decrease (127 mg twice daily eliglustat + 600 mg once daily rifampicin)	Not recommended	95% decrease (84 mg twice daily eliglustat + 600 mg once daily rifampicin)	Not recommended

\*The Summary of Product Characteristics (SmPC) does not provide specific guidance on the eliglustat dose for poor metabolisers taking a strong or moderate CYP2D6 inhibitor. The guidance only identifies when the standard dose should be modified due to potential interaction. Thus, the standard dose for poor metabolisers (84 mg once daily) is recommended. Since the CYP2D6 pathway is already non-functional in poor metabolisers and they are entirely dependent upon the CYP3A pathway for eliglustat metabolism, taking a CYP2D6 inhibitor is of no consequence in these patients. AUC: area under the curve.

treated by physicians without clinical experience of the condition should be evaluated by an expert offering specialized investigations for assessing Gaucher disease at least once each year.

For the patient choosing between eliglustat and enzyme therapy, it is essential that there is an informed consensus between patient and physician to consider social, familial, professional, and psychological factors, in the context of the patient's eligibility based on CYP2D6 genotyping, comorbidities, and potential for drug interaction set out in detail below. An algorithm to determine eligibility for eliglustat therapy is provided in Fig. 1.

#### 4.1. CYP2D6 genotyping

For patients who wish to be considered for eliglustat therapy, to predict their CYP2D6 metaboliser status and appropriate dosing,

determination of the CYP2D6 genotype by testing a blood sample at a nationally accredited laboratory is obligatory. Eliglustat is approved in the European Union for adult patients who are predicted to be extensive, intermediate or poor metabolisers. Eliglustat is not approved for the small subset of patients in whom genotyping indicates CYP2D6 ultra-rapid and indeterminate metabolism, since these patients may not reach adequate eliglustat concentrations to achieve a therapeutic effect. Local Sanofi Genzyme representatives can be contacted for information about suitably accredited local or central laboratories for CYP2D6 genotype testing in constituent European countries.

#### 4.2. Concomitant medications

Once CYP2D6 metaboliser status has been predicted from CYP2D6 genotyping to be extensive, intermediate, or poor, concomitant

**Table 3**  
Other potential drug interactions with eliglustat.

Drug class or drug name	Examples	Effect on concomitant agent's exposure	Recommendations for use concomitantly with eliglustat
<i>Agents whose concentrations may be increased by eliglustat:</i>			
P-gp substrates	Digoxin, colchicine, dabigatran, phenytoin, pravastatin	Digoxin: $C_{max}$ : 1.7-fold ↑ AUC <sub>last</sub> : 1.5-fold ↑ (eliglustat 127 mg twice daily + single 0.25 mg dose of digoxin)	Lower doses of the P-gp substrate drug and titration to therapeutic effect may be required
CYP2D6 substrates	Metoprolol, tricyclic antidepressants (e.g. nortriptyline, amitriptyline, imipramine, and desipramine), phenothiazines, dextromethorphan, atomoxetine	Metoprolol: $C_{max}$ 1.5-fold ↑ AUC: 2.1-fold ↑ (eliglustat 127 mg twice daily + single 50 mg dose of metoprolol)	Lower doses of the CYP2D6 substrate drug and titration to therapeutic effect may be required
<i>Antiarrhythmic agents:</i>			
Class IA antiarrhythmic drugs	Quinidine	NA	Avoid eliglustat
Class III antiarrhythmic drugs	Amiodarone, sotalol	NA	Avoid eliglustat

medications must be reviewed, as dose modifications are required for concomitant use of eliglustat with other drugs also metabolised by CYP2D6 and CYP3A (Tables 2 and 3). In addition to the examples of concomitant medications shown in these tables, treating physicians should consult the Summary of Product Characteristics of the required medication. Further sources of information include appropriate drug interaction databases (for example, Stockley's Drug Interactions, 8th edition at <https://ilmufarmasis.files.wordpress.com/2011/07/stockley-drug-interaction-2008.pdf> or the University of Washington Drug Interaction Database at <http://didb.druginteractioninfo.org>). Several drug interaction databases are available electronically. However, the physician should verify the quality and reliability of the database and preferably should use one that is familiar and that allows for correct interpretation of the data obtained.

#### 4.3. Pregnancy, lactation, and fertility

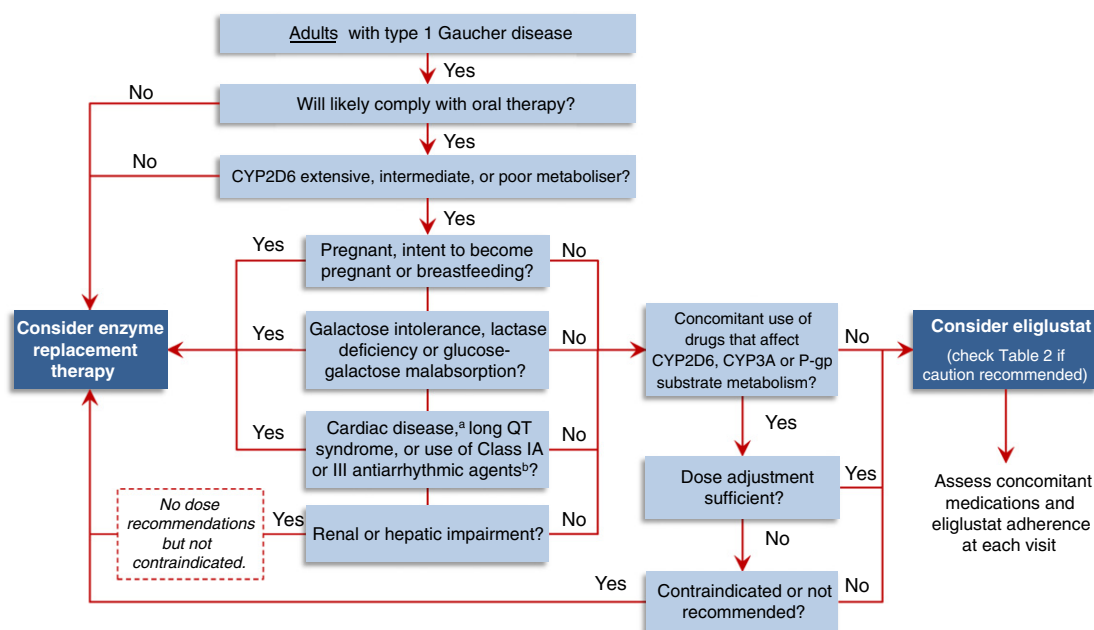
Currently, no data are available on the use of eliglustat in pregnant women. So far, animal studies do not suggest harmful effects with respect to reproductive toxicity. Women should avoid eliglustat during pregnancy and should be instructed to consult a Gaucher disease physician if they become pregnant while taking the drug. It is not known whether eliglustat or its metabolites are excreted in human milk, though pharmacodynamic and toxicological studies have shown eliglustat excretion in the milk of animals. The eliglustat product label recommends deciding whether to discontinue breast-feeding or to discontinue/abstain from eliglustat therapy after weighing the benefits of breast-feeding for the child and the benefits of therapy for the woman. Given that enzyme therapy during pregnancy and lactation has been shown to reduce complications of Gaucher disease without associated congenital defects or adverse effects [41–44], it is prudent for pregnant or breastfeeding women to use enzyme therapy. It is not known whether eliglustat has effects on male fertility in humans, although, when given in very high doses (10-fold greater than predicted human exposure) to rats, seminiferous epithelial degeneration and segmental hypoplasia of the testes and reversible inhibition of spermatogenesis were observed [1].

#### 4.4. Cardiac status

A cardiac evaluation at baseline, including an electrocardiogram (ECG), is already recommended in the ICGG Gaucher management recommendations [4]. When considering eliglustat, the ECG has additional relevance as a means to exclude underlying cardiac disease, and a cardiologist should be consulted if ECG changes or abnormalities are detected or suspected. The potential for adverse effects of eliglustat on cardiac conduction and repolarization requires substantially increased plasma concentrations (i.e. 11-fold the exposure at therapeutic doses), which may only be achieved through an overdose or a severe interaction with other medications metabolised by CYP2D6 and/or CYP3A. It is currently recommended to avoid the use of eliglustat in patients with certain cardiac conditions, in particular those predisposing to arrhythmias (e.g. recent acute myocardial infarction, ventricular arrhythmia, long QT syndrome, bradycardia, heart block, congestive heart failure) and in combination with Class IA and Class III antiarrhythmic medicinal products (Table 3). Use of eliglustat in these cardiac conditions has not been studied in clinical trials. Although no significant PR, QRS and QTc increases were seen in a thorough ECG study of healthy volunteers [45], more data are needed to evaluate the effects (or lack thereof) of eliglustat on cardiac conduction in these patients in the real world setting. Furthermore, cardiac examination, including ECG, would be prudent in patients taking a high number of concomitant medications (e.g. more than 4 or 5 drug classes), because potential drug interactions in this setting would be difficult to predict. Here, an opinion from and involvement of a cardiologist should be considered.

#### 4.5. Renal and hepatic status

Eliglustat has not been studied in patients with renal or hepatic impairment, and so no dose recommendations are offered in the product label, but generally the drug should be used with extreme caution, if at all, in such patients. Eliglustat is principally metabolised by the liver and is primarily excreted in faeces and to a lesser extent in urine. Given the proven effectiveness of enzyme therapy and the absence of effects on kidney and liver function, it is prudent to use enzyme therapy in patients with renal or hepatic impairment until satisfactory data have



<sup>a</sup> Congestive heart failure, recent acute myocardial infarction, bradycardia, heart block, ventricular arrhythmia.

<sup>b</sup> Class IA (e.g. quinidine) and Class III (e.g. amiodarone, sotalol)

Fig. 1. Algorithm for eliglustat eligibility in adults with type 1 Gaucher disease.

been collected demonstrating the safety of eliglustat in these populations. Similarly, no data are available in patients infected with hepatitis B or C virus or human immunodeficiency virus (HIV). In the first two diseases, reduced capacity of the liver to metabolise eliglustat is a concern. Eliglustat therapy can be considered in those without manifest hepatic impairment, provided there is close clinical monitoring of serum liver-related tests during treatment with concomitant medications.

#### 4.6. Special populations

A few special populations warrant consideration. Children were excluded from the clinical trials and only two adolescents were enrolled. A paediatric trial is planned to assess the efficacy and safety of eliglustat use in children and adolescents. Likewise, only a small number of patients aged 65 years and over were enrolled in the clinical trials and the efficacy and safety of eliglustat in these patients was comparable to patients younger than 65 years. Particular attention should be given to treating patients in this older group due to the high probability of co-morbidities and use of medications. Since the drug contains lactose as an excipient, patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take eliglustat [1].

#### 4.7. Recommendations for initial assessment

1. To determine any patient's eligibility for eliglustat treatment based on his or her CYP2D6 metaboliser status, CYP2D6 genotyping is mandatory. Eliglustat is extensively metabolised by CYP2D6, and, to a lesser extent, by the CYP3A isozyme of the cytochrome P450 pathway.
2. It is essential to assess concomitant use of medications or herbal supplements (including grapefruit products and other fruits that inhibit CYP3A) that might affect CYP2D6 and CYP3A metabolism (Tables 2 and 3).
3. Dosing of eliglustat is based on the patient's CYP2D6 metaboliser status and modified according to chronic use of concomitant medications also metabolised by CYP2D6 and CYP3A.
4. Screening for pregnancy, lactation, or intent to become pregnant is required, as eliglustat should be avoided during pregnancy and lactation.
5. Screening for cardiac, hepatic, and renal disease is required, as eliglustat is not recommended or should be used with caution in patients with these conditions.
6. Eliglustat is a capsule taken once or twice daily. It is important to assess the patient's ability to adhere strictly to daily oral treatment.
7. Treatment for Gaucher disease should be initiated and supervised by a physician with practical experience and familiarity with Gaucher disease.

### 5. Ongoing monitoring of patients taking eliglustat

In addition to existing recommendations for the ongoing monitoring of haematological, visceral, skeletal, and biochemical parameters in type 1 Gaucher disease [4], guidance specific to monitoring patients on eliglustat therapy is provided below.

#### 5.1. Clinical response to eliglustat

As shown in Table 1, eliglustat improves haematological and visceral disease parameters in previously untreated patients with type 1 Gaucher disease [27–29,31,34] and maintains haematological, visceral and bone parameters in patients whose disease has been stabilised by recent prior treatment with ERT [32]. Currently, there are no data which indicate that switching from eliglustat to ERT, or vice versa, will result in improvement in patients who do not achieve or maintain therapeutic goals for haemoglobin concentration, platelet count or spleen or liver

volumes within the expected time frames defined by Pastores et al. [3]. However, such a stratagem seems reasonable given the comparatively limited experience with eliglustat to date. Before changing therapies, patients should be thoroughly re-assessed including consideration of pre-treatment indicators of irreversible manifestations, concurrent illness or pregnancy, and the possibility of medication non-adherence or undisclosed concomitant medications. Any change of treatment must be prescribed after a complete and rigorous evaluation of the disease, including clinical and biological evaluation, biomarkers, and imaging – otherwise it will be difficult to attribute or not a complication to the new treatment.

When switching from ERT to eliglustat, in clinical trials there was no wash-out period between stopping ERT and starting eliglustat. It is thus reasonable to start eliglustat within 2 weeks after the last ERT infusion. There are no data to indicate antibody development to eliglustat and, to our knowledge, such a phenomenon has not been reported. However, since eliglustat is a small, orally active molecule and does not depend on protein targeting to the macrophage system for its mode of action, it may provide a useful alternative for patients who develop infusion reactions and/or attenuated therapeutic responses to enzyme therapy as a result of antibody formation. When switching patients from miglustat to eliglustat, it will be important to evaluate and document any adverse events, particularly neurological, prior to the switch, because unwanted effects on the nervous system, such as tremor or peripheral neuropathy, are side effects of miglustat and could persist after the drug is stopped.

As with any newly approved drug, attention to adverse events and monitoring for longer-term complications are important clinical responsibilities as well as regulatory obligations. In a pooled analysis of two randomized controlled trials and one 4-year clinical study with a total of 152 patients ages 16–69 years who received eliglustat for a median duration of 51.9 weeks (range 0.1 to 210.9 weeks), adverse reactions reported in >2% of the patients were headache, nausea, diarrhoea, abdominal pain, flatulence, arthralgia, and fatigue [46]. In the placebo-controlled pivotal trial of eliglustat, incidences of diarrhoea and abdominal pain were reported to be higher with placebo than with eliglustat [29].

#### 5.2. Concomitant medications

Assessment of concomitant medications (and intake of grapefruit products) that affect CYP2D6 and CYP3A metabolism at each visit is essential, because dosing of eliglustat is based on CYP2D6 metaboliser status and modified according to chronic use of concomitant medications also metabolised by CYP2D6 and CYP3A (Tables 2 and 3). Patients should be instructed to inform other treating physicians that they are taking eliglustat and that it may have interactions with drugs metabolised through these pathways. Where concomitant prescribing is necessary, required medications should be evaluated for potential interactions. Patients should also be advised to consult with a physician before use of any “over-the counter” medication, herbal substances, and any medication not routinely prescribed.

#### 5.3. Medication adherence

Unlike ERT, where infusions are commonly performed in a clinical setting and staff can monitor adherence to therapy, patients will be responsible for taking eliglustat each day. Physicians will need to ask patients about medication adherence at regular visits and emphasize the importance of taking eliglustat as directed.

Monitoring of eliglustat concentrations in blood is not useful for routine assessment of medication adherence due to the very rapid metabolism of eliglustat. However, there may be unusual circumstances where measurement of eliglustat blood levels would be indicated, such as in the face of highly divergent extremes of body mass and in cases of accidental co-exposure, suspected toxicity (e.g. cardiac events or arrhythmias), use of concomitant medications without known

interactions, emerging renal failure or jaundice, or bizarre symptoms in the patient otherwise unexplained. Such testing is available from the manufacturer of the drug (Sanofi Genzyme) and should be considered on a case-by-case basis. When monitoring eliglustat blood concentrations, it would be essential to record the time since the last eliglustat dose was taken to judge the effect of metabolism.

#### 5.4. Cardiac status

Routine ECG for patients taking eliglustat is not required as eliglustat is not predicted to cause increases in ECG intervals at therapeutic doses. If a PR, QRS or QTc prolongation is suspected or there are doubts regarding a patient's ECG findings, a cardiologist should be consulted for cardiac evaluation.

#### 5.5. Surgery

As coagulation abnormalities due to disease-related impaired production and chronic consumption of coagulation factors may occur even in ERT-treated Gaucher patients, evaluation for coagulation abnormalities should be routine, especially prior to surgical, dental, and obstetric procedures [47]. For patients taking eliglustat, physicians should also consider the potential for drug interactions between eliglustat and medications administered during surgical procedures. In emergent situations, it would be prudent temporarily to stop treatment with eliglustat.

#### 5.6. Recommendations for ongoing monitoring

1. The frequency of monitoring of Gaucher disease patients is dependent upon whether the patient has achieved therapeutic goals [3].
2. Patients taking eliglustat who do not achieve or maintain therapeutic goals within the expected time frames defined by Pastores et al. [3], should be thoroughly re-assessed and consideration given to switching to ERT.
3. It is important to assess concomitant use of medications and herbal supplements that affect CYP2D6 and CYP3A metabolism (including grapefruit and other fruit products that inhibit CYP3A) at every visit, because dosing of eliglustat is based on the patient's CYP2D6 metaboliser status and modified according to chronic use of concomitant medications also metabolised by CYP2D6 and CYP3A. Patients should consult their physicians before taking any new medication.
4. Where there is doubt as to whether the patient is taking the doses as instructed, they should be asked specifically about their adherence to prescribing guidance (i.e. compliance).

## 6. Summary

As a first-line therapy for type 1 Gaucher disease, eliglustat offers eligible patients a convenient, daily, oral therapy as an alternative to enzyme infusions. It is essential that Gaucher disease physicians carefully assess individual patients to determine their appropriateness for this oral therapy as set out in Fig. 1 and continue to monitor their response to eliglustat and use of concomitant medications to ensure the best possible outcome.

### Author contributions

All authors contributed equally to the development of this manuscript through their participation in the Eliglustat Advisory Board Meeting and subsequent involvement in drafting the manuscript and revising it critically for important intellectual content. NB and TMC agree to be accountable for the accuracy and integrity of the manuscript. All authors read and approved the final manuscript for publication.

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The authors did not receive funding for their participation in writing this manuscript. An initial meeting of the authors to consider and reach consensus on the appropriate use of eliglustat in the treatment of adults with type 1 Gaucher disease was convened and paid for by Sanofi Genzyme.

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