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Eliglustat Therapy and *CYP2D6* Genotype

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Introduction

Eliglustat (brand name CERDELGA) is a glucosylceramide synthase inhibitor used in the treatment of Gaucher disease (GD). Eliglustat is indicated for the long-term treatment of adult individuals with Gaucher disease type 1 (GD1) who are CYP2D6 normal metabolizers, intermediate metabolizers, or poor metabolizers as detected by an FDA-cleared test (1).

Gaucher disease is an autosomal recessive metabolic disorder characterized by accumulation of glucosylceramide (a sphingolipid also known as glucocerebroside) within lysosomes. This is caused by a malfunction of the enzyme acid beta-glucosidase, encoded by the gene GBA. Type 1 GD may present in childhood or adulthood with symptoms including bone disease, hepatosplenomegaly, thrombocytopenia, anemia and lung disease and –– unlike Gaucher types 2 and 3 –– does not directly affect the central nervous system primarily (2). Eliglustat, a ceramide mimic, inhibits the enzyme that synthesizes glucosylceramides (UDP-Glucose Ceramide Glucosyltransferase), thereby reducing the accumulation of these lipids in the lysosome (3).

Eliglustat is broken down to inactive metabolites by CYP2D6 and, to a lesser extent, CYP3A (3). The dosage of eliglustat is based on the individual's CYP2D6 metabolizer status. Individuals with normal CYP2D6 activity are termed normal metabolizers (NM), those with reduced activity are termed intermediate metabolizers (IM), and if activity is absent, poor metabolizers (PM).

The FDA-approved drug label for eliglustat provides specific dosage guidelines based on their CYP2D6 status and concomitant usage of CYP2D6 or CYP3A inhibitors, and states that hepatic and renal function should also be considered when determining the appropriate dosage (Table 1). The label also states that CYP2D6 ultrarapid metabolizers (UM) may not achieve adequate concentrations of eliglustat for a therapeutic effect, and that for individuals for whom a CYP2D6 genotype cannot be determined, a specific dosage cannot be recommended (1).

Dosing recommendations for eliglustat have also been published by the Dutch Pharmacogenetics Working Group (DPWG) based on CYP2D6 metabolizer type (Table 2) and include dose adjustments for dosing eliglustat with medications that alter CYP2D6 and or CYP3A function (Table 3).

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Table 1. The FDA Recommended Eliglustat Dosage Regimen by CYP2D6 Metabolizer Status (2020)

CYP2D6 metabolizer status	Eliglustat dosage
Ultrarapid metabolizer	May not achieve adequate concentrations
Normal metabolizer	84 mg twice daily
Intermediate metabolizer	84 mg twice daily
Poor metabolizer	84 mg once daily
Indeterminate metabolizer	Specific dosage cannot be recommended

For dose alterations based on decreased hepatic function, see Therapeutic Recommendations based on Genotype
This FDA table is adapted from (1).

Table 2. The DPWG Recommended Dosing of Eliglustat based on *CYP2D6* Phenotype (2018)

Phenotype	Implications for eliglustat therapy	Recommendation
CYP2D6 intermediate metabolizer	This gene variation reduces the conversion of eliglustat to inactive metabolites. This increases the risk of side effects, such as a (small, dose-dependent) elongation of the QT interval. The CYP3A inhibitors increase this risk even further.	No co-medication –– use the standard dose of 84 mg twice daily. Co-medication with a moderate or strong CYP2D6 or CYP3A inhibitor or strong CYP3A inducer: see Table 3.
CYP2D6 poor metabolizer		No co-medication –– use a dose of 84 mg once daily. Co-medication with a CYP3A inhibitor or strong CYP3A inducer: see Table 3.
CYP2D6 ultrarapid metabolizer	This gene variation increases the conversion of eliglustat to inactive metabolites. As a result, a normal dose is not effective. There is not enough scientific substantiation to suggest an effective dose for all ultrarapid metabolizers	Eliglustat is contraindicated. Choose an alternative if possible.

For dosage recommendations that incorporate co-medications and altered hepatic function, please see Therapeutic Recommendations based on Genotype
This DPWG table is adapted from (4) DPWG: Dutch Pharmacogenetics Working Group

Table 3. The DPWG Adjusted Daily Dosage for Eliglustat 84 mg based on Co-medications and Altered Hepatic Function (2018)

Co-medication(s)	Relative strength of CYP inhibitor/inducer	IM	PM
CYP2D6 inhibitor	Strong[1]	Once daily	--
	Moderate[2]	Once daily[#]	--
CYP3A inhibitor	Strong[3]	Once daily[#]	CI
	Moderate[4]	Once daily[#]	CI
	Weak[5]	--	Once daily[#]
CYP3A inducer	Strong[6]	CI	CI

Table 3. continued from previous page.

Co-medication(s)	Relative strength of CYP inhibitor/inducer	IM	PM
CYP2D6 inhibitor with CYP3A inhibitor	Strong[1], strong[3]	CI	--
	Strong[1], moderate[4]	CI	--
	Moderate[2], strong[3]	CI	--
	Moderate[2], moderate[4]	CI	--

CI: Contraindicated, IM: Intermediate Metabolizer, PM: Poor metabolizer
[1] Strong CYP2D6 inhibitor: for example, paroxetine, fluoxetine, quinidine, bupropion.
[2] Moderate CYP2D6 inhibitor: for example, duloxetine, terbinafine, moclobemide, mirabegron, cinacalcet, dronedarone.
[3] Strong CYP3A inhibitor: for example, ketoconazole, clarithromycin, itraconazole, cobicistat, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, posaconazole, voriconazole, telithromycin, conivaptan, boceprevir.
[4] Moderate CYP3A inhibitor: for example, erythromycin, ciprofloxacin, fluconazole, diltiazem, verapamil, aprepitant, atazanavir, darunavir, fosamprenavir, imatinib, cimetidine.
[5] Weak CYP3A inhibitor: amlodipine, cilostazol, fluvoxamine, goldenseal, isoniazid, ranitidine, ranolazine
[6] Strong CYP3A inducer: rifampicin, carbamazepine, phenobarbital, phenytoin, rifabutin, hypericum
[#] Individual requires additional monitoring for side effects.
DPWG guidelines available here (4) DPWG: Dutch Pharmacogenetics Working Group

Drug: Eliglustat

Eliglustat (brand name Cerdelga) is an oral substrate reduction therapy, indicated for the long-term treatment of adults with GD1 who are CYP2D6 NMs, IMs or PMs as detected by an FDA-approved test. Eliglustat is a selective substrate inhibitor of glucosylceramide synthase (3, 5). Eliglustat is an oral therapy alternative to injection perfusion enzyme replacement therapy (ERT) for the long-term treatment of GD1.

Gaucher disease is an inborn error of metabolism and lysosomal storage disorder. It is a rare monogenic, autosomal recessive disorder due to biallelic variant of the *GBA* gene, which encodes the lysosomal enzyme acid beta-glucosidase. Loss of acid beta-glucosidase function results in accumulation of glucosylceramide within the lysosome. Gaucher disease is divided into 3 major clinical types (types 1, 2 and 3) and 2 subtypes (perinatal-lethal form—a subtype of GD type 2 [GD2], and cardiovascular form—a subtype of GD type 3[GD3]). Gaucher disease type 1 is characterized by bone disease, hepatosplenomegaly, thrombocytopenia, anemia, lung disease and a distinct lack of primary CNS disease (in contrast with GD2 and GD3, which present with primary CNS involvement). Gaucher disease type 1 presents in childhood with bone disease occurring in 70–100% of individuals; this bone disease ranges from asymptomatic osteopenia to focal lytic or sclerotic lesions and osteonecrosis. However, bone disease may be the most debilitating aspect of GD1. Liver enlargement and cytopenia are also both very common, nearly universal (2, 6). Biochemical testing of GBA1 enzyme activity in peripheral blood is the gold standard to confirm GD diagnosis; molecular sequencing approaches are limited due to significant sequence identity between *GBA* and a pseudogene, *GBAP* (2, 7).

Eliglustat is a ceramide analog that specifically inhibits UDP-glucose ceramide glucosyltransferase, which catalyzes the first glycosylation step in glycosphingolipid biosynthesis (transfer of glucose to ceramide) (3, 7). Inhibition of the ceramide glycosyltransferase reduces the burden of glucosylceramides, which have been shown to accumulate in the lysosomes of GD individuals.

Eliglustat is metabolized primarily by CYP2D6 and, to a lesser extent, CYP3A. No active metabolites are known (3). Metabolized eliglustat is excreted through the urinary and gastrointestinal tracts. The CYP2D6 metabolizer status must be considered when determining the appropriate dosage of eliglustat; NMs, IMs, and PMs with normal hepatic and renal function can take the recommended dosage. Ultrarapid metabolizers "may not achieve adequate concentrations of eliglustat to achieve therapeutic effect." (1) Dosage levels cannot be recommended for individuals of undetermined CYP2D6 metabolizer status. Individuals who are CYP2D6 NMs concomitantly

taking CYP2D6 inhibitors, with moderate or severe hepatic impairment, or mild hepatic impairments and CYP2D6 inhibitor use should not take eliglustat. Both IMs and PMs taking CYP2D6 or CYP3A inhibitors, or both, demonstrating hepatic impairment are also contraindicated from eliglustat use.

Potential risk of cardiac arrhythmias should be considered in individuals taking eliglustat with CYP2D6 or CYP3A inhibitors, with certain metabolizer status and with varying degrees of hepatic impairment. More moderate adverse reactions in individuals during clinical trials included abdominal pain, diarrhea, flatulence, and back/extremity pain and were reported at least once in over 80% of individuals (8). Headache, arthralgia, fatigue and nausea have also been reported at least once in >60% of individuals, but one study found no correlation between CYP2D6 metabolizer status and frequency of these adverse events (8). Real world evidence for use of eliglustat shows most individuals tolerate long-term treatment without adverse effects (9).

Use of eliglustat during pregnancy has not been sufficiently studied to assess drug-associated risks of major birth defects, spontaneous abortion, or other adverse maternal/fetal outcomes. "Women with Gaucher disease type 1 have an increased risk of spontaneous abortion, especially if disease symptoms are not treated and controlled pre-conception and during a pregnancy. Pregnancy may exacerbate existing Gaucher disease type 1 symptoms or result in new disease manifestations. Gaucher disease type 1 manifestations may lead to adverse pregnancy outcomes including, hepatosplenomegaly which can interfere with the normal growth of a pregnancy and thrombocytopenia which can lead to increased bleeding and possible hemorrhage" (1). There are no human data available on the presence of eliglustat in human milk, effects on the breastfed infant, or effects on milk production. Based on animal studies, it is likely that eliglustat would be present in human milk (1).

Eliglustat has not been sufficiently studied for safety and effectiveness in pediatric individuals or subjects over 65. Individuals with renal impairment should be dosed based on their CYP2D6 metabolizer status. Individuals with hepatic impairment should similarly be dosed in light of CYP2D6 metabolizer status and concomitant use of CYP2D6 or CYP3A inhibitors (1).

Gene: *CYP2D6*

The cytochrome P450 superfamily (CYP450) is a large and diverse group of enzymes that form the major system for metabolizing lipids, hormones, toxins, and drugs in the liver. The *CYP450* genes are very polymorphic and can result in decreased, absent, or increased enzyme activity. The CYP2D6 enzyme is responsible for the metabolism of many commonly prescribed drugs, including antidepressants, antipsychotics, analgesics, and beta-blockers.

CYP2D6 Alleles

The *CYP2D6* gene on chromosome 22q13.2 is highly polymorphic. Over 100 star (*) alleles have been described and cataloged at the Pharmacogene Variation (PharmVar) Consortium, and each allele is associated with either normal, decreased, or absent enzyme function (Table 4) (10). In addition to the wildtype *CYP2D6*1* allele, variant *CYP2D6* alleles (or haplotypes) can harbor single nucleotide polymorphisms (SNPs), insertions or deletions, gene conversions, as well as copy number variations.

The combination of *CYP2D6* alleles that a person has is used to determine their diplotype (for example, *CYP2D6 *4/*4*). Based on function, each allele can be assigned an activity score from 0 to 1, which in turn is often used to assign a phenotype (for example, CYP2D6 poor metabolizer). However, the activity score system is not standardized across clinical laboratories or *CYP2D6* genotyping platforms. The CPIC revised their activity scoring guidelines in October 2019 to promote harmonization. The *CYP2D6* phenotype is defined by the sum of the 2 allele activity scores, which is most commonly in the range of 0 to 3.0 (11):

- An UM has an activity score greater than 2.25
- A NM phenotype has an activity score of 1.25–2.25

- An IM has an activity score of >0–1.25
- A PM has an activity score of 0 (14)

Table 4. Activity Status of Selected *CYP2D6* Alleles

Allele type	*CYP2D6* alleles
Normal function	*1, *2, *27, *33
Decreased function	*10, *17, *41, *49
No function	*3, *4, *5, *6, *36

For a comprehensive list of *CYP2D6* alleles, please See PharmVar.

The *CYP2D6*1* allele is considered the wildtype allele when no variants are detected and is associated with normal enzyme activity and the "normal metabolizer" phenotype. In addition, the *CYP2D6*2*, **27*, and **33* alleles are also considered to have near-normal activity.

Other *CYP2D6* alleles include variants that produce a non-functioning enzyme (for example, **3*, **4*, **5*, and **6*) (12, 13, 14, 15) or an enzyme with decreased activity (for example, **10*, **17*, and **41*) (16, 17, 18) (see Table 4). There are large inter-ethnic differences in the frequency of these alleles, with **3*, **4*, **5*, **6*, and **41* being more common in Caucasians, **17* more common in Africans, and **10* more common in Asians (19).

Allele Frequencies Vary between Populations

Among Asians and in individuals of Asian descent, only approximately 50% of *CYPD6* alleles are normal function, and the frequency of *CYP2D6* duplications is as high as 45%, although this may have been overestimated by not accounting for tandem hybrid alleles (for example, **36+*10*) (20). Other studies of a US individual population suggested less than 50% of alleles detected within Asian-descent individuals are normal function alleles in a single copy, with 30% of alleles arising from structural variants (duplications or deletions) (21). Common no-function variants are *CYP2D6*36* and *CYP2D6*4* (21). Both these alleles contain the variant "c.100C>T" (see Allele Nomenclature table) (19, 20, 22, 23). The *CYP2D6*36* allele is the result of a gene conversion event with the pseudogene *CYP2D7* (24). This no-function allele is most commonly found in individuals of Asian ancestry (21).

Among Africans and African-Americans, only approximately 50% of *CYP2D6* alleles are normal function (12, 18, 19, 25). African-Americans also have been found to have a higher frequency of no-function structural variants or decreased function single-copy variant alleles versus Caucasian or Hispanic-Americans (21).

Middle Eastern countries show a great diversity in phenotypic and allelic distribution for *CYP2D6* (26), though on average, these individuals show a lower frequency of PM phenotypes (0.91%) and higher UM phenotypes (11.2%) than other ethnicities (Note: Oceania and Middle Eastern ethnicities combined in this study) (27).

Among European countries, there is diversity of allelic distribution (28). Gene duplications were more common in the south-eastern countries (Greece, Turkey: 6%) and less common in north-western countries (Sweden and Denmark, <1%). Meanwhile, *CYP2D6*4* and **5* alleles were generally more common in the north and less common in the south. (28) Worldwide *CYP2D6* genotype and phenotype frequencies have been catalogued and recently published (27).

CYP2D6 Phenotype

***CYP2D6* Phenotype Frequencies Vary between Populations**

Normal metabolizers: Approximately 77–92% of individuals have 2 normal function alleles (**1* or **2*), or one normal function allele and one decreased function allele. These individuals are "normal metabolizers" and are most likely to have a phenotypically normal response to the drug.

Intermediate metabolizers: Approximately 2–11% of individuals are IMs—they have either 2 decreased function alleles or one normal or decreased function and one no allele (27). A study of a diverse US urban population of children found that roughly 8% of subjects were IMs (29), Within the US, it has been observed that individuals of African or Asian descent were most likely to be classified as IMs (20–28% of population by ethnicity) (21).

Poor metabolizers: Approximately 5–10% of individuals are PMs—they have 2 no alleles (30). The PMs are more commonly found in European Caucasians and their descendants. The no *CYP2D6*4* and **5* alleles largely account for the PM phenotype in these populations (14, 17, 31). It should be noted that the frequency of PMs can be much lower in certain populations including East Asian, Oceania and Middle Eastern (27). Studies of US multi-ethnic populations have estimated the prevalence of PM to be between 1.5–5.7% (21, 29).

Ultrarapid metabolizers: Individuals who are UMs have at least 3 copies of the *CYP2D6* gene. The UM phenotype has been estimated to be present in 1–2% of individuals, but the prevalence varies widely in different populations. It is estimated to be present in up to 28% of North Africans, Ethiopians, and Arabs; up to 10% in Caucasians; 3% in African-Americans, and up to 1% in Hispanics, Chinese, and Japanese (30, 32). The UMs made up 9% of subjects in an urban multi-ethnic population with a large portion of Hispanic/Latino subjects (29). A larger study of US individuals predicted a UM phenotype in only 2.2% of individuals, regardless of ethnicity (21).

Linking Gene Variation with Treatment Response

Genetic variation in the *CYP2D6* gene can influence whether an individual achieves adequate concentrations of eliglustat and therapeutic benefit (namely, CYP2D6 ultrarapid metabolizers) or is at an increased risk of adverse events (namely, CYP2D6 poor metabolizers). Eliglustat dose, metabolizer status/genotype and concomitant CYP inhibitor medication use should all be considered in assessing potential risk of cardiac arrhythmias. Conditions that decrease the clearance of eliglustat put individuals in this elevated risk category (namely, hepatic impairment, CYP2D6 IMs or PMs taking CYP inhibitors), for complete information please see (1).

Six GD individuals in the International Collaborative Gaucher Group Gaucher Registry who were known UMs voluntarily reported their 1–3 year outcomes after taking eliglustat. This included individuals who had been on ERT and switched to eliglustat as well as some who were treatment naive. For these individuals, the reported dosages were 84 mg 3 times daily (4 individuals) or twice daily (2 individuals). Four of the 6 individuals maintained hemoglobin concentration and platelet counts within the therapeutic goal range after 2 years; however, one individual developed anemia and another developed moderate thrombocytopenia. One individual reported discontinuation of eliglustat (rationale unclear). Adverse events and reasons for discontinuation of therapies are not recorded within the Registry; however, very few individuals of any metabolizer status discontinued treatment with eliglustat over the course of this study (22/231, 9%). (9)

Genetic Testing

The NIH Genetic Testing Registry provides examples of the genetic tests that are available for eliglustat response and for the *CYP2D6* gene.

The *CYP2D6* is a particularly complex gene that is difficult to genotype due to highly homologous neighboring pseudogenes, as well as the large number of variants and the presence of gene deletions, duplications, and multiplications. The complexity of genetic variation complicates making a correct determination of *CYP2D6* genotype.

Targeted genotyping typically includes up to 30 variant *CYP2D6* alleles (over 100 alleles have been identified so far). Test results are reported as a diplotype, such as *CYP2D6 *1/*1*. However, it is important to note that the

number of variants tested can vary among laboratories, which can result in diplotype result discrepancies between testing platforms and laboratories (33).

A result for copy number, if available, is also important when interpreting *CYP2D6* genotyping results. Gene duplications and multiplications can be denoted by "xN", for example: *CYP2D6*1xN* with *xN* representing the number of *CYP2D6* gene copies. Note representation of duplications is also not standardized among laboratories.

If the test results include an interpretation of the individual's predicted metabolizer phenotype, such as "*CYP2D6 *1/*1*, normal metabolizer", this may be confirmed by checking the diplotype and assigning an activity score to each allele (for example, 0 for no, 0.5 for decreased function, and 1.0 for each copy of a normal function allele, Table 4). See the *CYP2D6* alleles section above for more information.

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2018 Statement from the US Food and Drug Administration (FDA):

The recommended dosage of Eliglustat in adults is based on the patient's CYP2D6 metabolizer status.

[…]

Reduce dosage frequency of Eliglustat 84 mg to once daily in CYP2D6 NMs and IMs with or without hepatic impairment taking CYP2D6 or CYP3A inhibitors.

Table [5] : Recommended Dosage of Eliglustat: 84 mg Once Daily based on CYP2D6 Metabolizer, Hepatic Impairment Status, and Concomitant CYP Inhibitors

CYP2D6 Metabolizer Status	Hepatic Impairment Status	Concomitant CYP Inhibitor
NMs	Without Hepatic Impairment	Taking a strong or moderate CYP2D6 inhibitor Taking a strong or moderate CYP3A inhibitor
	Mild (Child-Pugh Class A) Hepatic Impairment	Taking a weak CYP2D6 inhibitor Taking a strong, moderate, or weak CYP3A inhibitor
IMs	Without hepatic involvement	Taking a strong or moderate CYP2D6 inhibitor

4 CONTRAINDICATIONS

Eliglustat is contraindicated in the following patients based on CYP2D6 metabolizer status due to the risk of cardiac arrhythmias from prolongation of the PR, QTc, and/or QRS cardiac intervals.

NMs

- Taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor
- Moderate or severe hepatic impairment
- Mild hepatic impairment and taking a strong or moderate CYP2D6 inhibitor

IMs

[1] The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug. Certain terms, genes and genetic variants may be corrected in accordance with nomenclature standards, where necessary. We have given the full name of abbreviations, shown in square brackets, where necessary.

- Taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor
- Taking a strong CYP3A inhibitor Any degree of hepatic impairment

PMs

- Taking a strong CYP3A inhibitor
- Any degree of hepatic impairment

7 DRUG INTERACTIONS

7.1 Effect of other drugs on Eliglustat

Coadministration of Eliglustat with:

- CYP2D6 or CYP3A inhibitors may increase eliglustat concentrations which may increase the risk of cardiac arrhythmias from prolongation of the PR, QTc, and/or QRS cardiac interval.
- strong CYP3A inducers decreases eliglustat concentrations which may reduce efficacy.

Table [6] : Prevention and Management Strategies of Drug Interactions Affecting eliglustat based on CYP2D6 Metabolizer status and Concomitant Interacting drug

Concomitant Drug(s)	CYP2D6 Metabolizer Status		
	NMs	IMs	PMs
CYP2D6 Inhibitor			
Strong	Reduce frequency of eliglustat 84mg to once daily		Continue eliglustat 84mg once daily*
Moderate			
Weak	Continue eliglustat 84mg twice daily		
CYP3A Inhibitor			
Strong	Reduce frequency of eliglustat 84 mg to once daily	Contraindicated	
Moderate		Avoid coadministration.	
Weak	Continue eliglustat 84mg twice daily		Avoid coadministration.
CYP2D6 Inhibitor Concomitantly with a strong CYP3A Inhibitor			
Strong	Contraindicated		
Moderate			
CYP2D6 Inhibitor Concomitantly with a moderate CYP3A Inhibitor			
Strong	Contraindicated		Avoid coadministration
Moderate			
CYP3A Inducer			
Strong	Avoid coadministration		

* No effect of CYP2D6 inhibitor due to little or no CYP2D6 activity in CYP2D6 PMs.

8 Use In Specific Populations

8.6 Renal Impairment

Use eliglustat in patients with renal impairment based on the patient's CYP2D6 metabolizer status

NMs

- Avoid eliglustat in patients with end-stage renal disease (ESRD) (estimated creatinine clearance (eCLcr) less than 15 mL/min not on dialysis or requiring dialysis).
- No dosage adjustment is recommended in patients with mild, moderate, or severe renal impairment (eCLcr at least 15 mL/min).

IMs and PMs

Avoid eliglustat in patients with any degree of renal impairment.

8.7 Hepatic Impairment

Use eliglustat in patients with hepatic impairment based on CYP2D6 metabolizer status and concomitant use of CYP2D6 or CYP3A inhibitors

NMs

Eliglustat is contraindicated in patients with [see Contraindications]:

- severe (Child-Pugh Class C) hepatic impairment
- moderate (Child-Pugh Class B) hepatic impairment
- mild (Child-Pugh Class A) hepatic impairment taking a strong or moderate CYP2D6 inhibitor

Reduce dosage frequency of eliglustat 84 mg to once daily [see Dosage and Administration] in patients with mild hepatic impairment taking:

- a weak CYP2D6 inhibitor
- a strong, moderate, or weak CYP3A inhibitor

No dosage adjustment is recommended in patients with mild hepatic impairment, unless otherwise specified above.

IMs and PMs

Eliglustat is contraindicated in patients with any degree of hepatic impairment [see Contraindications].

Please review the complete therapeutic recommendations that are located here: (1).

2018 Summary of recommendations from the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP)

CYP2D6 UM:

Eliglustat is contra-indicated.

1 choose an alternative if possible

CYP2D6 IM:

Recommendation:

- Co-medication with BOTH a MODERATE to STRONG CYP2D6 INHIBITOR AND a MODERATE to STRONG CYP3A INHIBITOR: Eliglustat is contra-indicated.
  1 choose an alternative if possible

Strong CYP2D6 inhibitor: for example paroxetine, fluoxetine, quinidine, bupropione. Moderate CYP2D6 inhibitor: for example duloxetine, terbinafine, moclobemide, mirabegron, cinacalcet, dronedarone. Strong

CYP3A inhibitor: for example ketoconazole, clarithromycin, itraconazole, cobicistat, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, posaconazole, voriconazole, telithromycin, conivaptan, boceprevir. Moderate CYP3A inhibitor: for example erythromycin, ciprofloxacin, fluconazole, diltiazem, verapamil, aprepitant, atazanavir, darunavir, fosamprenavir, imatinib, cimetidine.

- Co-medication with a STRONG CYP2D6 INHIBITOR (e.g. paroxetine, fluoxetine, quinidine, bupropione):
  1 use a dose of 84 mg eliglustat 1x daily
- Co-medication with a MODERATE CYP2D6 INHIBITOR (for example duloxetine, terbinafine, moclobemide, mirabegron, cinacalcet, dronedarone):
  1. consider a dose of 84 mg eliglustat 1x daily
  2. be alert to side effects
- Co-medication with a STRONG CYP3A INHIBITOR (for example ketoconazole, clarithromycin, itraconazole, cobicistat, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, posaconazole, voriconazole, telithromycin, conivaptan, boceprevir):

-1. choose an alternative if possible

- if an alternative is not an option:
- consider a dose of 84 mg eliglustat 1x daily
- be alert to side effects
  - Co-medication with a MODERATE CYP3A INHIBITOR (for example erythromycin, ciprofloxacin, fluconazole, diltiazem, verapamil, aprepitant, atazanavir, darunavir, fosamprenavir, imatinib, cimetidine):
    1. choose an alternative
    2. if an alternative is not an option:
       1. consider a dose of 84 mg eliglustat 1x daily
       2. be alert to side effects
  - Co-medication with a STRONG CYP3A INDUCER (for example rifampicin, carbamazepine, phenobarbital, phenytoin, rifabutine, hypericum): Eliglustat is not recommended. The plasma concentration may decrease so sharply that a therapeutic effect cannot be achieved.
    1 choose an alternative if possible
  - NO co-medication with a moderate or strong CYP2D6 or CYP3A inhibitor or strong CYP3A inducer:
    1 use the standard dose of 84 mg 2x daily

CYP2D6 PM:

Recommendation:

- Co-medication with a STRONG CYP3A INHIBITOR (for example ketoconazole, clarithromycin, itraconazole, cobicistat, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, posaconazole, voriconazole, telithromycin, conivaptan, boceprevir):

Eliglustat is contra-indicated.

1 choose an alternative if possible
  - Co-medication with a MODERATE CYP3A INHIBITOR (for example erythromycin, ciprofloxacin, fluconazole, diltiazem, verapamil, aprepitant, atazanavir, darunavir, fosamprenavir, imatinib, cimetidine):

Eliglustat is not recommended.

1 choose an alternative if possible
- Co-medication with a WEAK CYP3A INHIBITOR (for example amlopidine [amlodipine], cilostazole [cilostazol], fluvoxamine, goldenseal, isoniazide [isoniazid], ranitidine, ranolazine):
  1. choose an alternative for the weak CYP3A inhibitor if possible
  2. if an alternative is not an option:
     1. use a dose of 84 mg eliglustat 1x daily
     2. be alert to side effects
- Co-medication with a STRONG CYP3A INDUCER (for example rifampicin, carbamazepine, phenobarbital, phenytoin, rifabutine, hypericum):

Eliglustat is not recommended. The plasma concentration may decrease so sharply that a therapeutic effect cannot be achieved.

1 choose an alternative if possible
- NO co-medication with a CYP3A inhibitor or strong CYP3A inducer:
  1 use a dose of 84 mg 1x daily

Please review the complete therapeutic recommendations that are located here:(4).

Nomenclature for Selected *CYP2D6* Alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*2*	2851C>T (Arg296Cys)	NM_000106.6:c.457G>C	NP_000097.3:p.Arg296Cys	rs16947
	4181G>C (Ser486Thr)	NM_000106.6:c.886C>T	NP_000097.3:p.Ser486Thr	rs1135840
*CYP2D6*3*	2550delA (Arg259fs)	NM_000106.6:c.775delA	NP_000097.3:p.Arg259fs	rs35742686
*CYP2D6*4*	1846G>A	NM_000106.6:c.506-1G>A	Variant occurs in a non-coding region (splice variant causes a frameshift)	rs3892097
*CYP2D6*5*	Variant results in a whole gene deletion			
*CYP2D6*6*	1707 del T (Trp152Glyfs) CYP2D6T	NM_000106.6:c.454delT	NP_000097.3:p.Trp152Glyfs	rs5030655
*CYP2D6*10*	100C>T (Pro34Ser)	NM_000106.6:c.886T>C	NP_000097.3:p.Pro34Ser	rs1065852
*CYP2D6*17*	1023C>T[1] (Thr107Ile)	NM_000106.6:c.1457G>C	NP_000097.3:p.Thr107Ile	rs28371706
	2851C>T[2] (Arg296Cys)	NM_000106.6:c.457G>C	NP_000097.3:p.Arg296Cys	rs16947
	4181G>C (Ser486Thr)	NM_000106.6:c.886C>T	NP_000097.3:p.Ser486Thr	rs1135840
*CYP2D6*27*	3854G>A (Glu410Lys)	NM_000106.6:c.1319G>A	NP_000097.3:p.Glu410Lys	rs769157652

Table continued from previous page.

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*31*	2851C>T (Arg296Cys)	NM_000106.6:c.1457G>C	NP_000097.3:p.Arg296Cys	rs16947
	4043G>A (Arg440His)	NM_000106.6:c.454delT	NP_000097.3:p.Arg440His	rs267608319
	4181G>C (Ser486Thr)	NM_000106.6:c.100C>T	NP_000097.3:p.Ser486Thr	rs1135840
*CYP2D6*36*[3]	100C>T (Pro34Ser)	NM_000106.6:c.320C>T	NP_000097.3:p.Pro34Ser	rs1065852
	4129C>G (Pro469Ala)	NM_000106.6:c.1405C>G	NP_000097.3:p.Pro469Ala	rs1135833
	4132A>G (Thr470Ala)	NM_000106.6:c.1408A>G	NP_000097.3:p.Thr470Ala	rs1135835
	4156C>T+4157A>C (His478Ser)	NM_000106.6:c.1432C>T + NM_000106.6:c.1433A>C	NP_000097.3:p.His47Ser	rs28371735 + rs766507177
	4159G>C (Gly479Arg)	NM_000106.6:c.1435G>C	NP_00097.3:p.Gly479Arg	
	4165T>G (Phe481Val)	NM_000106.6:c.1441T>G	NP_00097.3:p.Phe481Val	
	4168G>A+4169C>G (Ala482Ser)	NM_000106.6:c.1444G>A + NM_000106.6:c.1445C>G	NP_000097.3:p.Ala482Ser	rs74478221 + rs75467367
	4181G>C (Ser486Thr)	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
*CYP2D6*41*	2851C>T (Arg296Cys)	NM_000106.6:c.457G>C	NP_000097.3:p.Arg296Cys	rs16947
	2988G>A	NM_000106.6:c.985+39G>A	Variant occurs in a non-coding region (impacts splicing).	rs28371725
*CYP2D6*49*	100C>T (Pro34Ser)	NM_000106.6:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
	1612T>A (Phe120Ile)	NM_00106.6:c.358T>A	NP_000097.3:p.Phe120Ile	rs1135822
	4181G>C (Ser486Thr)	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840

[1] In the literature, 1023C>T is also referred to as 1111C>T
[2] In the literature, 2851C>T is also referred to as 2938C>T
[3] *CYP2D6*36* is a gene conversion with *CYP2D7;* variants provided here are from the Pharmacogene Variation Consortium.
Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting (34).
Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS).
Nomenclature for Cytochrome P450 enzymes is available from the Pharmacogene Variation (PharmVar) Consortium.

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