CYP2D6: eliglustat 6137/6138/6139

AUC = 'area under the time-concentration curve', CTCAE = common terminology criteria for adverse events, ECG = electrocardiogram, IM = intermediate metaboliser (gene dose 0.25-1) (decreased CYP2D6 enzyme activity), NM = normal metaboliser (gene dose 1.25-2.5) (normal CYP2D6 enzyme activity), PBPK = physiologically based pharmacokinetic, PKPD = pharmacokinetic-pharmacodynamic, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), SmPC = Summary of Product Characteristics, $t_{1/2}$ = elimination half-live, UM = ultra-rapid metaboliser (gene dose ≥ 2.75) (increased CYP2D6 enzyme activity)

Disclaimer: The Pharmacogenetics Working Group of the KNMP formulates the optimal recommendations for each phenotype group based on the available evidence. If this optimal recommendation cannot be followed due to practical restrictions, e.g. therapeutic drug monitoring or a lower dose is not available, the health care professional should consider the next best option.

Brief summary and justification of choices:
Eliglustat is predominantly metabolised into inactive metabolites by CYP2D6 and to a lesser extent by CYP3A. Eliglustat is an inhibitor of CYP2D6 and P-gp. Thus, eliglustat inhibits its own metabolism by inhibiting CYP2D6. This results in a nonlinear dose-concentration relationship.
Because eliglustat is predominantly metabolised by CYP2D6, genetic variants that decrease the CYP2D6 activity (poor and intermediate metaboliser (PM and IM)) increase the systemic exposure to eliglustat at a given dose. Similarly, genetic variants that increase the CYP2D6 activity (ultra-rapid metaboliser, UM) decrease the systemic exposure to eliglustat at a given dose.

PM The systemic exposure following 84 mg twice daily at steady state is 7- to 9-fold higher in PM. Because a PK/PD model predicts small increases in the PR-, QRS- and QTcF-interval at eliglustat plasma concentrations 11-fold the expected C_{max} in humans, a dose reduction for PM from 84 mg twice daily to 84 mg once daily is included in the label of eliglustat. The KNMP: Pharmacogenetics Working Group concluded that there is a gene-drug interaction and therapy adjustment is required (yes/yes-interaction). The therapeutic recommendations are based on the European and American SmPCs.

IM For one IM, the AUC was 2- to 4-fold higher than the AUCs of the NM with the highest and lowest AUC respectively. This difference is too small for recommendation of a dose reduction. However, for IM, eliglustat is also not recommended in case of mild hepatic impairment and/or in case of mild, moderate or severe renal impairment. The KNMP Pharmacogenetics Working Group concluded that there is a gene-drug interaction and that a warning is required in case of mild hepatic impairment and/or mild, moderate or severe renal impairment (yes/yes-interaction). The therapeutic recommendations are based on the European and American SmPCs.

UM Four UM, for which the dose was titrated up to eliglustat 127 mg twice daily, had an adequate clinical response on eliglustat. For the only UM receiving eliglustat 84 mg twice daily, the clinical response was not adequate. Because of the small number of UM in which a daily dose of 254 mg has been proven to be effective, the KNMP Pharmacogenetics Working Group decided to follow the SmPC recommendation of an alternative for UM (yes/yes-interaction). The reason is that part of the UM have more than 3 active CYP2D6 alleles and a correspondingly higher CYP2D6 activity. Moreover, also comedication with inducers of CYP3A can result in an additional increase in eliglustat clearance.

You can find an overview of the clinical and kinetic effects per phenotype in the background information text of the gene-drug interactions in the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

Recommendation concerning pre-emptive genotyping, including justification of choices:
Due to the absence of publications of new clinical studies or case reports with patients with a CYP2D6 genotype leading to reduced or increased CYP2D6 activity in medical journals, and thus the absence of evidence of an increase in adverse events code ≥ D (grade ≥ 3) in these patients, the clinical implication of the gene-drug interaction scores only 2 out of the maximum of 10 points (with pre-emptive genotyping considered to be potentially beneficial for scores ranging from 0 to 2 points) (see also the Clinical Implication Score tables at the end of this risk analysis). However, there is not enough evidence to reject the warnings and recommendations in the SmPC. In addition, the Clinical Implication Score is mainly (for 80%) based on studies published in medical journals and therefore not suited to determine the clinical implication for gene-drug interactions for which data are only provided by pre-registration

studies. For these reasons, the KNMP Pharmacogenetics Working Group decided to ignore the Clinical Implication Score and adopt the genotyping recommendation in the SmPC. The SmPC indicates that genotyping must be performed before starting eliglustat to guide drug and dose selection. This would amount to genotyping being essential for drug safety according to the nomenclature of the KNMP Pharmacogenetics Working Group.

Source	Code	Effect	Comments
ref. 1 Ruskin JN et al. How a concentration-effect analysis of data from the eliglustat thorough electrocardiographic study was used to support dosing recommendations. Mol Genet Metab 2020;131:211-8. PMID: 33012655.	3 1 IM: AA PM: AA	Predictions from pharmacokinetic/pharmacodynamic-ECG modelling based on the thorough ECG study in 47 healthy adult volunteers indicated below, together with other exposure-related factors, contributed to the CYP2D6 phenotype-based dosing recommendations for eliglustat, including dose adjustments and contraindications when co-administered with drugs metabolized by the CYP-2D6 and CYP3A pathways. The ECG study was a double-blind cross-over study in which 42 healthy volunteers received 4 different single doses in randomised order: placebo, 169 mg eliglustat (therapeutic dose), 675 mg eliglustat (supratherapeutic dose), and 400 mg moxifloxacin (positive control (a dose shown to prolong QT/QTc interval by 8 to 13 ms)). The other 5 volunteers completed only part of the study. Drugs of abuse; alcohol, caffeine-containing products; grapefruit and grapefruit juice; and medications and/or dietary supplements known to prolong QT/QTc interval or inhibit or induce CYP2D6 were excluded. Triplicate ECGs were determined at 3 timepoints before dosing and 18 timepoints in the period of 0.5-22.5 hour after dosing. Plasma concentrations were determined before and up to 36 hours after dosing. For QTcF (QT interval corrected with Fridericia's correction formula), a linear mixed-effect model was used and included period, sequence, treatment, sex, and time as fixed effects; baseline QTcF (the averaged value of all three ECGs performed before dosing) as a covariate; and time-by-treatment and sex-by-treatment interactions, and with subject nested within sequence as a random effect. If the upper bound of the one-sided 95% CI for the increase in QTcF (QT-interval corrected with Fridericia's correction formula) from baseline for eliglustat minus the increase in QTcF from baseline for placebo fell below 10 ms, it was concluded that the exposure associated with this dose of eliglustat did not prolong the QTc interval to a clinically significant degree. The relationship between placebo-corrected change from baseline in QTc interval (i.e., QTcF), heart rate, PR and QRS intervals (calculated for each subject and at each time point), and plasma eliglustat concentrations was explored using a linear mixed-effect model with plasma concentration as a fixed effect and subject as a random effect. If the P value of the population slope was < 0.05, a linear relationship was declared and the predicted mean increases from baseline (along with two-sided 95% CI) were calculated using the geometric means of observed C_{max} for the two doses of eliglustat tested in the study, as well as the geometric means of physiologically-based pharmacokinetic model-predicted C_{max} in different drug-drug interaction scenarios (i.e., eliglustat with strong CYP2D6 and/or strong CYP3A inhibitors). Assuming a within-subject standard deviation of 9 ms, a total of 36 subjects (9 subjects per treatment sequence) were calculated to be required to detect an 8-ms difference in QTc between placebo and active treatment with a power of 95% and one-sided type 1 error of 2.5%. Genotyping: - 45x NM+IM - 2x PM Results: - No volunteer had QTcF ≥480 ms, QTcF change from baseline > 60 ms, QRS interval ≥ 120 ms, or met the PR outlier criterion (PR > 200 ms and increase from baseline ≥25%).	

ref. 1, continuation

- No serious adverse events, severe adverse events, or deaths occurred during the study, and no subjects withdrew because of an adverse event.
- Treatment-emergent adverse events considered possibly or probably related to eliglustat treatment reported by two or more subjects included dizziness (5 subjects), nausea (3 subjects), headache (2 subjects), blurred vision (2 subjects), and abdominal pain/abdominal pain lower (2 subjects). The majority of treatment-emergent adverse events were mild, and all resolved by study end. The number of subjects reporting at least 1 treatment-emergent adverse event was highest for 675 mg eliglustat (16 events, 8 subjects (17.8%)) and moxifloxacin (10 events, 7 subjects (16.7%)]) and was lowest for 167 mg eliglustat (8 events, 4 subjects (9.1%)) and placebo (5 events, 5 subjects (11.1%)). Two moderate adverse events of vasovagal episodes (coded to vasovagal syncope) were assessed as not related to eliglustat. Both cases were attributed temporally to phlebotomy.

Modelling results:

Drug-drug interaction scenarios depending on CYP2D6 phenotype	PBPK model-predicted mean eliglustat C_{max} (ng/mL)	PKPD-ECG predicted mean (90% confidence interval) (ms) (increase in baseline compared to placebo)		
		QTcF interval	PR interval	QRS interval
Normal metaboliser (84 mg twice daily)				
Eliglustat alone	21.5	0.3 (−1.1;1.6)	1.5 (0.3;2.7)	0.3 (−0.4;1.0)
With paroxetine (strong CYP2D6 inhibitor)	126	2.9 (1.6;4.3)	5.3 (4.1;6.5)	1.6 (0.9;2.3)
With ketoconazole (strong CYP3A inhibitor)	48.4	1.0 (−0.4;2.3)	2.5 (1.3;3.7)	0.7 (−0.0;1.4)
With paroxetine (strong CYP2D6 inhibitor) + ketoconazole (strong CYP3A inhibitor)	405	10.0 (8.3;11.6))	15.3 (13.9;16.8)	5.0 (4.3;5.8)
Intermediate metaboliser (84 mg twice daily)				
Eliglustat alone	54.4	1.1 (−0.2;2.5)	2.7 (1.5;3.9)	0.7 (0.0;1.4)
With paroxetine (strong CYP2D6 inhibitor)	135	3.2 (1.8;4.5)	5.6 (4.4;6.8)	1.7 (1.0;2.4)
With ketoconazole (strong CYP3A inhibitor)	217	5.2 (3.8;6.6)	8.6 (7.3;9.8)	2.7 (2.0;3.5)
With paroxetine (strong CYP2D6 inhibitor) + ketoconazole (strong CYP3A inhibitor)	464	11.4 (9.7;13.2)	17.5 (15.9;19.0)	5.8 (5.0;6.6)
Poor metaboliser (84mg once daily)				

ref. 1, continuation		Eliglustat alone	67.8	1.5 (0.1;2.8)	3.2 (2.0;4.4)	0.9 (0.2;1.6)	
		With ketoconazole (strong CYP3A inhibitor)	284	6.9 (5.4;8.4)	11.0 (9.7;12.3)	3.6 (2.8;4.3)	
		Note: The most conservative threshold established by regulatory authorities for eliglustat concentrations with no QT-related safety concerns was a mean C_{max} of 250 ng/mL					
ref. 2 SmPC Cerdelga (eliglustat) 28-08-23.	0	Indication: Cerdelga is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1) who are CYP2D6 poor metabolisers (PMs), intermediate metabolisers (IMs), or normal metabolisers (NMs). Dose: The recommended dose is 84 mg eliglustat twice daily in CYP2D6 intermediate metabolisers (IMs) and normal metabolisers (NMs). The recommended dose is 84 mg eliglustat once daily in CYP2D6 poor metabolisers (PMs). *Special populations* *CYP2D6 ultra-rapid metabolisers (URMs) and indeterminate metabolisers* Eliglustat should not be used in patients who are CYP2D6 ultra-rapid metabolisers (URMs) or indeterminate metabolisers. *Patients with hepatic impairment* In CYP2D6 normal metabolisers (NMs) with severe (Child-Pugh class C) hepatic impairment, eliglustat is contraindicated. In CYP2D6 normal metabolisers (NMs) with moderate hepatic impairment (Child-Pugh class B), eliglustat is not recommended. In CYP2D6 normal metabolisers (NMs) with mild hepatic impairment (Child-Pugh class A), no dosage adjustment is required and the recommended dose is 84 mg eliglustat twice daily. In CYP2D6 intermediate metabolisers (IMs) or poor metabolisers (PMs) with any degree of hepatic impairment, eliglustat is not recommended. *Patients with renal impairment* In CYP2D6 normal metabolisers (NMs) with mild, moderate or severe renal impairment, no dosage adjustment is required and the recommended dose is 84 mg eliglustat twice daily. In CYP2D6 NMs with end stage renal disease (ESRD), eliglustat is not recommended. In CYP2D6 intermediate metabolisers (IMs) or poor metabolisers (PMs) with mild, moderate or severe renal impairment or ESRD, eliglustat is not recommended. Contraindications: Patients who are CYP2D6 intermediate metabolisers (IMs) or normal metabolisers (NMs) taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor and patients who are CYP2D6 poor metabolisers (PMs) taking a strong CYP3A inhibitor. Use of Cerdelga under these conditions results in substantially elevated eliglustat plasma concentrations. Warning: *Initiation of therapy: CYP2D6 genotyping* Before initiation of treatment with Cerdelga, patients should be genotyped for CYP2D6 to determine the CYP2D6 metaboliser status. *Drug-drug interactions* Cerdelga is contraindicated in patients who are CYP2D6 intermediate metabolisers (IMs) or normal metabolisers (NMs) taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor, and in patients who are CYP2D6 poor metabolisers (PMs) taking a strong CYP3A inhibitor. For use of eliglustat with one strong or moderate CYP2D6 or CYP3A inhibitor, see Interactions. *Patients with hepatic impairment* Limited data are available in CYP2D6 normal metabolisers (NMs)					

ref. 2, continuation	IM: AA	with moderate hepatic impairment. Use of eliglustat in these patients is not recommended. Limited or no data are available in CYP2D6 intermediate metabolisers (IMs) or poor metabolisers (PMs) with any degree of hepatic impairment. Use of eliglustat in these patients is not recommended. *Patients with renal impairment* Limited or no data are available in CYP2D6 normal metabolisers (NMs), intermediate metabolisers (IMs) or poor metabolisers (PMs) with ESRD and in CYP2D6 intermediate metabolisers (IMs) or poor metabolisers (PMs) with mild, moderate, or severe renal impairment; use of eliglustat in these patients is not recommended. <u>Interactions</u>: The list of substances in this section is not an inclusive list and the prescriber is advised to consult the SmPC of all other prescribed medicinal products for potential drug-drug interactions with eliglustat. *Drugs that may increase eliglustat exposure* Cerdelga is contraindicated in patients who are CYP2D6 intermediate metabolisers (IMs) or normal metabolisers (NMs) taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor, and in patients who are CYP2D6 poor metabolisers (PMs) taking a strong CYP3A inhibitor. Use of Cerdelga under these conditions results in substantially elevated eliglustat plasma concentrations. *CYP2D6 inhibitors* *In intermediate (IMs) and normal metabolisers (NMs):* After repeated 84 mg twice daily doses of eliglustat in non-PMs, concomitant administration with repeated 30 mg once daily of paroxetine, a strong inhibitor of CYP2D6, resulted in a 7.3- and 8.9-fold increase in eliglustat C_{max} and AUC_{0-12h}, respectively. A dose of eliglustat 84 mg once daily should be considered when a strong CYP2D6 inhibitor (e.g. paroxetine, fluoxetine, quinidine, bupropion).is used concomitantly in IMs and NMs. At 84 mg twice daily dosing with eliglustat in non-PMs, it is predicted that concomitant use of moderate CYP2D6 inhibitors (e.g. duloxetine, terbinafine, moclobemide, mirabegron, cinacalcet, dronedarone) would increase eliglustat exposure approximately up to 4-fold. Caution should be used with moderate CYP2D6 inhibitors in IMs and NMs. *CYP3A inhibitors* *In intermediate (IMs) and normal metabolisers (NMs):* After repeated 84 mg twice daily doses of eliglustat in non-PMs, concomitant administration with repeated 400 mg once daily doses of ketoconazole, a strong inhibitor of CYP3A, resulted in a 3.8-fold and 4.3-fold increase in eliglustat C_{max} and AUC_{0-12h}, respectively; similar effects would be expected for other strong inhibitors of CYP3A (e.g. clarithromycin, ketoconazole, itraconazole, cobicistat, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, posaconazole, voriconazole, telithromycin, conivaptan, boceprevir). Caution should be used with strong CYP3A inhibitor in IMs and NMs. At 84 mg once daily dosing with eliglustat in non-PMs, it is predicted that concomitant use of moderate CYP3A inhibitors (e.g. erythromycin, ciprofloxacin, fluconazole, diltiazem, verapamil, aprepitant, atazanavir, darunavir, fosamprenavir, imatinib, cimetidine) would increase the eliglustat exposure approximately up to 3-fold. Caution should be used with moderate CYP3A inhibitors in IMs and NMs. *In poor metabolisers (PMs):* At 84 mg once daily dosing with eliglustat in PMs, it is predicted that concomitant use of strong CYP3A inhibitors (e.g. ketoconazole, clarithromycin, itraconazole, cobicistat, indinavir, lopinavir, ritonavir, saquinavir, telaprevir, tipranavir, posaconazole, voriconazole, telithromycin, conivaptan, boceprevir) would increase the C_{max} and AUC_{0-24} of eliglustat 4.3-fold and 6.2-fold. The use of	

ref. 2, continuation		strong CYP3A inhibitors is contraindicated in PMs. At 84 mg once daily dosing with eliglustat in PMs, it is predicted that concomitant use of moderate CYP3A inhibitors (e.g. erythromycin, ciprofloxacin, fluconazole, diltiazem, verapamil, aprepitant, atazanavir, darunavir, fosamprenavir, imatinib, cimetidine) would increase the C_{max} and AUC_{0-24} of eliglustat 2.4- and 3.0-fold, respectively. Use of a moderate CYP3A inhibitor with eliglustat is not recommended in PMs. Caution should be used with weak CYP3A inhibitors (e.g. amlopidine, cilostazol, fluvoxamine, goldenseal, isoniazid, ranitidine, ranolazine) in PMs. *CYP2D6 inhibitors used simultaneously with CYP3A inhibitors* *In intermediate (IMs) and normal metabolisers (NMs):* At 84 mg twice daily dosing with eliglustat in non-PMs, it is predicted that the concomitant use of strong or moderate CYP2D6 inhibitors and strong or moderate CYP3A inhibitors would increase C_{max} and AUC_{0-12} up to 17- and 25-fold, respectively. The use of a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor is contraindicated in IMs and NMs. *Agents that may decrease eliglustat exposure* *Strong CYP3A inducers* After repeated 127 mg twice daily doses of eliglustat in non-PMs, concomitant administration of repeated 600 mg once daily doses of rifampicin (a strong inducer of CYP3A as well as the efflux transporter P-gp) resulted in an approximately 85% in eliglustat exposure. After repeated 84 mg twice daily doses of eliglustat in PMs, concomitant administration of repeated 600 mg once daily doses of rifampicin resulted in an approximately 95% decrease in eligustat exposure. Use of a strong CYP3A4 inducer (e.g. rifampin, carbamazepine, phenobarbital, phenytoin, rifabutin and St. John's Wort) with eliglustat is not recommended in IMs, NMs and PMs. <u>Pharmacodynamics</u>: *Clinical efficacy and safety* The recommended dosing regimens are based on modelling, either using the PK/PD data from the dose-titration regimens applied in the clinical studies for IMs and NMs, or using the physiologically-based PK data for PMs. *Clinical experience in CYP2D6 poor metabolisers (PMs) and ultra-rapid metabolisers (URMs)* There is limited experience with Cerdelga treatment of patients who are PMs or URMs. In the primary analysis period of the three clinical studies, a total of 5 PMs and 5 URMs were treated with Cerdelga. All PMs received eliglustat 42 mg twice daily, and four of these (80%) had an adequate clinical response. The majority of URMs (80%) received a dose escalation to 127 mg eliglustat twice daily, all of which had adequate clinical responses. The one URM	
	UM: A	who received 84 mg twice daily did not have an adequate clinical response. The predicted exposures with 84 mg eliglustat once daily in patients who are PMs are expected to be similar to exposures observed with 84 mg eliglustat twice daily in CYP2D6 intermediate metabolisers (IMs). Patients who are URMs may not achieve adequate concentrations to achieve a therapeutic effect. No dosing recommendation for URMs can be given. <u>Pharmacokinetics</u>: Following repeated dosing of eliglustat 84 mg twice daily in non-PMs and once daily in PMs, steady state was reached by 4 days, with an accumulation ratio of 3-fold or less.	
	PM: A	After repeated oral doses of 84 mg eliglustat twice daily, eliglustat elimination half-life is approximately 4-7 hours in non-PMs and 9 hours in PMs. *Characteristics in specific groups* *CYP2D6 phenotype* Population pharmacokinetic analysis shows that the CYP2D6 predicted phenotype based on genotype is the most important	

<table>
<tr><td>ref. 2, continuation</td><td></td><td>factor affecting pharmacokinetic variability. Individuals with a CYP-2D6 poor metaboliser predicted phenotype (approximately 5-10% of the population) exhibit higher eliglustat concentrations than intermediate or normal CYP2D6 metabolisers.
Hepatic impairment:
Effects of mild and moderate hepatic impairment were evaluated in a single dose phase 1 study. After a single 84 mg dose, eliglustat C_{max} and AUC were 1.2- and 1.2-fold higher in CYP2D6 normal metabolisers (NMs) with mild hepatic impairment, and 2.8- and 5.2-fold higher in CYP2D6 normal metabolisers (NMs) with moderate hepatic impairment compared to healthy CYP2D6 normal metabolisers (NMs).
After repeated 84 mg twice daily doses of Cerdelga, C_{max} and AUC_{0-12} are predicted to be 2.4- and 2.9-fold higher in CYP2D6 normal metabolisers (NMs) with mild hepatic impairment and 6.4- and 8.9-fold higher in CYP2D6 normal metabolisers (NMs) with moderate hepatic impairment compared to healthy CYP2D6 normal metabolisers (NMs).
After repeated 84 mg once daily doses of Cerdelga, C_{max} and AUC_{0-24} are predicted to be 3.1- and 3.2 -fold higher in CYP2D6 normal metabolisers (NMs) with moderate hepatic impairment compared to healthy CYP2D6 normal metabolisers (NMs) receiving Cerdelga 84 mg twice daily.
Steady state PK exposure could not be predicted in CYP2D6 intermediate metabolisers (IMs) and poor metabolisers (PMs) with mild and moderate hepatic impairment due to limited or no single-dose data. The effect of severe hepatic impairment was not studied in subjects with any CYP2D6 phenotype.
Renal impairment:
Effect of severe renal impairment was evaluated in a single dose phase 1 study. After a single 84 mg dose, eliglustat C_{max} and AUC were similar in CYP2D6 normal metabolisers (NMs) with severe renal impairment and healthy CYP2D6 normal metabolisers (NMs). Limited or no data were available in patients with ESRD and in CYP2D6 intermediate metabolisers (IMs) or poor metabolisers (PMs) with severe renal impairment.</td><td></td></tr>
<tr><td>ref. 3
SmPC Cerdelga (eliglustat), USA, 29-08-18.</td><td>0

UM: AA</td><td><u>Indication</u>:
Cerdelga is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1) who are CYP2D6 normal metabolizers (NMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test.
Limitations of use:
• Patients who are CYP2D6 ultra-rapid metabolizers (URMs) may not achieve adequate concentrations of Cerdelga to achieve a therapeutic effect.
• A specific dosage cannot be recommended for those patients whose CYP2D6 genotype cannot be determined (indeterminate metabolizers).
<u>Dosage</u>:
Patient selection
Select patients with Gaucher disease type 1 based on their CYP-2D6 metabolizer status. It is recommended patient genotypes be established using an FDA-cleared test for determining CYP2D6 genotype.
Recommended adult dosage
The recommended dosage of Cerdelga in adults is based on the patient’s CYP2D6 metabolizer status.
Table 1: Recommended Dosage Regimen by CYP2D6 Metabolizer Status
<table>
<tr><td>CYP2D6 Metabolizer Status</td><td>CERDELGA Dosage</td></tr>
<tr><td>NMs</td><td rowspan="2">84 mg twice daily</td></tr>
<tr><td>IMs</td></tr>
<tr><td>PMs</td><td>84 mg once daily</td></tr>
</table>
Dosage adjustment in NMs and IMs with or without hepatic impairment and concomitant use of CYP2D6 or CYP3A Inhibitors
Reduce dosage frequency of Cerdelga 84 mg to once daily in CYP2D6 NMs and IMs with or without hepatic impairment taking CYP2D6 or CYP3A inhibitors, as shown in table 2.</td><td></td></tr>
</table>

ref. 3, continuation

Table 2: Recommended Dosage of CERDELGA 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 Impairment	• Taking a strong or moderate CYP2D6 inhibitor

Contraindications:

Cerdelga 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 CYP-2D6 inhibitor

IMs

- 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

Warnings:

Cerdelga is predicted to cause increases in ECG intervals (PR, QTc, and QRS) at substantially elevated eliglustat plasma concentrations and may increase the risk of cardiac arrhythmias.

- Use of Cerdelga is contraindicated, to be avoided, or requires dosage adjustment in patients taking CYP2D6 or CYP3A inhibitors, depending CYP2D6 metabolizer status, type of inhibitor, or degree of hepatic impairment [see Dosage, Contraindications, and Drug interactions].

Drug interactions:

Coadministration of Cerdelga 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 Cerdelga efficacy.

See Table 3 for prevention and management of interactions with drugs affecting Cerdelga.

Use of Cerdelga is contraindicated, to be avoided, or may require dosage adjustment depending on the concomitant drug and CYP2D6 metabolizer status.

Table 3: Prevention and Management Strategies of Drug Interactions Affecting Cerdelga Based on CYP2D6 Metabolizer Status and Conco-mitant Interacting	CYP2D6 Metabolizer Status		
	NMs	IMs	PMs

ref. 3, continuation		DrugConcomitant Drug(s)			
		CYP2D6 Inhibitor			
		Strong	Reduce frequency of Cerdelga 84 mg to once daily		Continue Cerdelga 84 mg once daily[a]
		Moderate			
		Weak	Continue Cerdelga 84 mg twice daily		
		CYP3A Inhibitor			
		Strong	Reduce frequency of Cerdelga 84 mg to once daily	Contraindicated	
		Moderate		Avoid coadministration	
		Weak	Continue Cerdelga 84 mg 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[a]
		Moderate			
		CYP3A Inducer			
		Strong	Avoid coadministration		
		[a] No effect of CYP2D6 inhibitor due to little or no CYP2D6 activity in CYP2D6 PMs.			
		Use in specific populations:			
		Renal Impairment			
		Use Cerdelga in patients with renal impairment based on the patient's CYP2D6 metabolizer status.			
		NMs			
		• Avoid Cerdelga 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 Cerdelga in patients with any degree of renal impairment.			
		Hepatic Impairment			
		Use Cerdelga in patients with hepatic impairment based on CYP-2D6 metabolizer status and concomitant use of CYP2D6 or CYP3A inhibitors.			
		NMs			
		• Cerdelga is contraindicated in patients with: - 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 Cerdelga 84 mg to once daily 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			
		• Cerdelga is contraindicated in patients with any degree of hepatic impairment.			
		Pharmacokinetics:			
	PM: A	*Absorption* In CYP2D6 NMs, the eliglustat pharmacokinetics is time-dependent and the systemic exposure increases in a more than dose proportional manner over the dose range of 42 to 294 mg (0.5 to 3.5 times the recommended dosage). In addition, after multiple oral doses of 84 mg twice daily in NMs, eliglustat systemic exposure (AUC_{0-12}) increased up to about 2-fold at steady state compared to after the first dose ($AUC_{0-\infty}$). The pharmacokinetics of eliglustat in CYP2D6 PMs is expected to be linear and time independent. Compared to NMs, the systemic exposure following 84 mg twice daily at steady state is 7- to 9-fold higher in PMs. Dosing of Cerdelga 84 mg once daily has not been studied in PMs.			AUC in comparison with NM: IM: 200-400% PM: 700-900%

ref. 3, continuation

IM: AA

The predicted C_{max} and $AUC_{0\text{-}24hr}$ in PMs using a physiologically based pharmacokinetic (PBPK) model with 84 mg once daily were 75 ng/mL and 956 hr·ng/mL, respectively.

Table 4 describes the pharmacokinetic parameters for eliglustat in healthy subjects following multiple doses of 84 mg CERDELGA twice daily.

Table 4: Pharmacokinetic Parameters for Eliglustat following Multiple Doses of 84 mg CERDELGA Twice Daily

Parameter	CYP2D6 Metabolizer Status		
	NMs (n=96)	IMs (n=1)	PMs[c] (n=9)
C_{max} (ng/mL)[a]	12.1 (42%) to 25.0 (141%)	44.6	113 (32%) to 137 (40%)
AUC_{tau} (ng·hr/mL)[a]	76.3 (37%) to 143 (160%)	306	922 (33%) to 1057 (38%)
Median T_{max} (hr) [min to max][b]	1.5 [0.5 to 3.0] to 2 [1.5 to 2.1]	2	3 [2 to 4]

[a] Range of the mean (CV%) values from multiple studies

[b] Range of the median time to reach maximum plasma concentration (Tmax) from multiple studies

[c] 84 mg twice daily is not the recommended dosage in PMs [see Dosage].

Elimination

Eliglustat terminal elimination half-life was approximately 6.5 hours in CYP2D6 NMs, and 8.9 hours in PMs.

Specific Populations

Patients with renal impairment

Eliglustat pharmacokinetics was similar in CYP2D6 NMs with severe renal impairment and healthy CYP2D6 NMs. Eliglustat pharmacokinetics in NMs with ESRD and in IMs or PMs with any degree of renal impairment is unknown.

Patients with hepatic impairment

The effect of hepatic impairment is highly variable with the coefficients of variation (CVs%) of 135% and 110% for C_{max} and 171% and 121% for AUC in CYP2D6 NMs with mild and moderate hepatic impairment, respectively.

Steady-state pharmacokinetics of eliglustat in CYP2D6 IMs and PMs with mild and moderate hepatic impairment is unknown. The effect of severe hepatic impairment in subjects with any CYP2D6 phenotype is unknown.

Drug interaction studies

Table 5 describes the effect of drug interactions on the pharmacokinetics of eliglustat.

Table 5: Drug Interactions Affecting Eliglustat Concentrations

Concomitant Drug(s)	CYP2D6 Metabolizer Status					
	NMs		IMs		PMs	
	C_{max}	AUC_{tau}	C_{max}	AUC_{tau}	C_{max}	AUC_{tau}
CYP2D6 Inhibitor						
Paroxetine (strong)	↑ 7.0-fold	↑ 8.4-fold	↑ 2.1-fold[a]	↑ 2.3-fold[a]	No increase expected[d]	
Terbinafine (moderate)	↑ 3.8-fold[a]	↑ 4.5-fold[a]	↑ 1.6-fold[a]			
CYP3A Inhibitor						
Ketoconazole (strong)	↑ 4.0-fold	↑ 4.4-fold	↑ 4.4-fold[a]	↑ 5.4-fold[a]	↑ 4.3-fold[a,b]	↑ 6.2-fold[a,b]
Fluconazole (moderate)	↑ 2.8-fold[a]	↑ 3.2-fold[a]	↑ 2.5-fold[a]	↑ 2.9-fold[a]	↑ 2.4-fold[a,b]	↑ 3.0-fold[a,b]
CYP2D6 Inhibitors Concomitantly with CYP3A Inhibitors						
Paroxetine with ketoconazole	↑ 16.7-fold[a]	↑ 24.2-fold[a]	↑ 7.5-fold[a]	↑ 9.8-fold[a]	Expected similar increase as with CYP3A inhibitors alone[d]	
Terbinafine with	↑ 10.2-fold[a]	↑ 13.6-fold[a]	↑ 4.2-fold[a]	↑ 5.0-fold[a]		

ref. 3, continuation		fluconazole						
		CYP3A Inducers						
		Rifampin (strong)	↓ 90%[c]				↓ 95%	

[a] Predicted pharmacokinetic parameters based on PBPK models
[b] Following coadministration with CERDELGA 84 mg once daily
[c] Following coadministration with CERDELGA 127 mg twice daily (1.5 times the recommended dosage)
[d] Due to little or no CYP2D6 activity in CYP2D6 PMs
↑ = Increased; ↓ = Decreased
No clinically significant pharmacokinetic changes were observed for eliglustat when coadministered with intravenous rifampin (an OATP inhibitor).

Risk group	IM with CYP2D6 inhibitors, IM and PM with CYP3A inhibitors, UM with CYP3A4-inducers

Comments:

- An article evaluating the effect of CYP2D6 phenotype on AUC of eliglustat was not included (Peterschmitt MJ et al. Safety, tolerability, and pharmacokinetics of eliglustat tartrate (Genz-112638) after single doses, multiple doses, and food in healthy volunteers. J Clin Pharmacol 2011;51:695-705. PubMed PMID: 20864621). The only PM in the study (n = 36, of which 12 received placebo and the remaining 24 healthy volunteers were divided over 3 dose groups (42 mg, 168 mg and 294 mg)) was randomized to the placebo group. AUC was determined after a single dose. Patients were divided over 5 phenotype groups, including 'intermediate to normal' and 'normal to ultra-rapid', that were not defined. It was not stated whether the calculated AUCs were corrected for dose.
  An article showing that with lower eliglustat doses (21 mg, 42 mg once daily) the PBPK model predicted exposure in IM and PM was within the outlined safety margin (C_{max} <250 ng/mL) when eliglustat was administered with ketoconazole, where the current recommendation is a contraindication of coadministration, was not included (Sahasrabudhe SA et al. Physiologically-based pharmacokinetic model development, validation, and application for prediction of eliglustat drug-drug interactions. Clin Pharmacol Ther 2022;112:1254-63. PMID: 36056771). The model was not based on new data, but on the eliglustat registration studies and the results from the modelling were not included in the SmPC, so do not add to the SmPC data.

Date of the literature search: 23 September 2023.

	Phenotype	**Code**	**Gene-drug interaction**	**Action**	**Date**
KNMP Pharmacogenetics Working Group decision	PM	1A	yes	yes	6 November 2023
	IM	1AA	yes	yes	
	UM	0A	yes	yes	

Mechanism:
Eliglustat is predominantly metabolised into inactive metabolites by CYP2D6 and to a lesser extent by CYP3A. Eliglustat is an inhibitor of CYP2D6 and P-gp. Thus, eliglustat inhibits its own metabolism by inhibiting CYP2D6. This results in a nonlinear dose-concentration relationship.

Clinical Implication Score:

Table 1: Definitions of the available Clinical Implication Scores

Potentially beneficial	PGx testing for this gene-drug pair is potentially beneficial. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guideline	0-2 +
Beneficial	PGx testing for this gene-drug pair is beneficial. It is advised to consider genotyping the patient before (or directly after) drug therapy has been initiated to guide drug and dose selection	3-5 +
Essential	PGx testing for this gene-drug pair is essential for drug safety or efficacy. Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection	6-10 +

Table 2: Criteria on which the attribution of Clinical Implication Score is based

Clinical Implication Score Criteria	Possible Score	Given Score
Clinical effect associated with gene-drug interaction (drug- or diminished efficacy-induced)		
• CTCAE Grade 3 or 4 (clinical effect score D or E)	+	
• CTCAE Grade 5 (clinical effect score F)	++	
Level of evidence supporting the associated clinical effect grade ≥ 3		
• One study with level of evidence score ≥ 3	+	
• Two studies with level of evidence score ≥ 3	++	
• Three or more studies with level of evidence score ≥ 3	+++	
Number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3		
• 100 < NNG ≤ 1000	+	
• 10 < NNG ≤ 100	++	
• NNG ≤ 10	+++	
PGx information in the Summary of Product Characteristics (SmPC)		
• At least one genotype/phenotype mentioned	+	
OR		
• Recommendation to genotype	++	++
OR		
• At least one genotype/phenotype mentioned as a contra-indication in the corresponding section	++	
Total Score:	10+	2+
Corresponding Clinical Implication Score:		Potentially beneficial
Score according to the SmPC:		Essential