CYP2D6: zuclopenthixol 1547/1548/1549

AUC = area under the concentration-time curve, Cl_{or} = oral clearance, C_{ss} = steady state concentration, 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), NS = non-significant, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), S = significant, SmPC = Summary of Product Characteristics, 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:
Zuclopenthixol is primarily metabolised by CYP2D6 to inactive metabolites. Correspondingly, all 7 studies with more than 10 patients showed a significant effect of gene variants altering CYP2D6 activity on (dose-corrected) zuclopenthixol exposure (Waade 2021, Tveito 2021, Van Berlo-van de Laar 2004, Jaanson 2002, Linnet 1996, Jerling 1996 and Dahl 1991). So, there is a gene-drug interaction. The only study investigating clinical outcomes (Jaanson 2002; 52 patients including 13x IM and 4x PM) found a numerically higher percentage of gene variants resulting in an inactive CYP2D6 enzyme in the group with extrapyramidal disorders and tardive dyskinesia, but significance was not reached. Van Berlo-van de Laar 2004 found a decrease in daily dose and an increase in the number of changes in dose for 11 IM. Because the rather small size of Jaanson 2002 could explain the lack of a significant effect, the increase in dose changes in Van Berlo-van de Laar 2004 suggests a clinical effect, and both adverse events and effectiveness of zuclopenthixol are known to be dose (and thus exposure) dependent, the KNMP Pharmacogenetics Working Group decided to recommend dose adjustments for patients with a CYP2D6 gene variant (yes/yes-interactions). QT-elongation and Torsade de Pointes have also been reported in zuclopenthixol users. Also the risk for these rare, but serious adverse events increases with increasing exposure.
Justification for the recommended dose adjustments:
Recommended dose adjustments were based on the weighted means of the observed zuclopentixol exposure compared to NM.

PM: The weighted mean of the calculated dose adjustment for a total of 40 PM is a dose reduction to 62% of the normal dose (median 60%, range 44%-69%). This was translated to 50% to be more achievable in clinical practice.

IM: The weighted mean of the calculated dose adjustment for a total of 122 IM is a dose reduction to 74% of the normal dose (median 72%, range 67%-76%). This was translated to 75% to be more achievable in clinical practice.

UM: The calculated dose adjustment based on one study with 2 UM is a dose increase to 150% of the normal dose (Patteet 2016). However, Tveito 2021 found a numerically much smaller effect on the geometric mean dose-corrected serum concentration compared to (NM+gene dose 1/0) for 14 UM on long-acting injectable zuclopenthixol and 2 UM on oral zuclopenthixol (dose increase to 102% of the normal dose based on the weighted mean of the observed exposure differences). This difference should be even smaller in comparison with NM instead of (NM+gene dose 1/0). The KNMP Pharmacogenetics Working Group concludes that there are not enough data to calculate a dose adjustment for UM. Considering the broad therapeutic range of zuclopenthixol (4-50 ng/ml (10-125 nmol/L) with > 100 ng/ml (249 nmol/L) considered to be toxic) and the lack of any studies providing indications for ineffectiveness in UM, recommending an alternative (so not to start zuclopenthixol) is too strong. For this reason, it is recommended to try a dose increase in case of ineffectiveness (not exceeding 1.5 times the normal dose).

You can find a detailed overview of the observed kinetic and clinical effects 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:
The KNMP Pharmacogenetics Working Group considers genotyping before starting zuclopenthixol to be potentially beneficial for the prevention of side effects and for effectiveness. Genotyping can be considered on an individual

patient basis. If, however, the genotype is available, the KNMP Pharmacogenetics Working Group recommends adhering to the gene-drug guideline.
The clinical implication of the gene-drug interaction scores 1 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):
No significant clinical effects were reported in users of zuclopenthixol with a variant phenotype. This results in a score of 0 out of the maximum of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (only points for CTCAE grade ≥ 3).
The lack of a clinical effect also results in a score of 0 of the maximum of 3 points for the second and third criterion of the clinical implication score: the level of evidence supporting an associated clinical effect grade ≥ 3 and the number needed to genotype (NNG) in the Dutch population to prevent one clinical effect code ≥ D (grade ≥ 3).
The Summaries of Product Characteristics (SmPCs) of zuclopenthixol mention the influence of CYP2D6 gene variants on zuclopenthixol metabolism, but do not mention the presence of a gene variant as a contraindication and do not recommend pre-emptive genotyping. This results in 1 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (1 point for at least one genotype/phenotype mentioned in the SmPC, but not mentioned as a contra-indication and no recommendation to genotype).

The table below follows the KNMP definitions for NM, PM, IM and UM. The definitions of NM, PM, IM and UM used in the table below may therefore differ from the definitions used by the authors in the article.

<table>
<tr><th>Source</th><th>Code</th><th>Effect</th><th>Comments</th></tr>
<tr><td>ref. 1
Waade RB et al.
Impact of CYP-2D6 on serum concentrations of flupentixol, haloperidol, perphenazine and zuclopenthixol.
Br J Clin Pharmacol 2021;87:2228-35.
PMID: 33118660.</td><td>4

PM: A
IM: A</td><td>248 patients were treated with oral zuclopenthixol. The data in this study were from the same database as the patients in Tveito 2021, so the patient group is very likely to include the oral zuclopenthixol group in Tveito 2021 or at least overlap with it. Therapeutic drug monitoring was routinely done. The mean number of measurements per patient was 2.5 for NM, 2.7 for IM and 3.2 for PM. Genotyping was performed either before or after treatment start. Due to the small number, UMs were not included. Trough serum concentrations were determined (10 to 26 hours after dosing). Only measured serum concentrations within the lower and upper limits of quantification were included.
Measurements were also excluded if the requisition forms (lacking for approximately 11% of measurements) provided information on possible noncompliance, or on use of co-medication inhibiting or inducing the CYP enzymes involved in zuclopenthixol metabolism.

Genotyping:
- 135x NM
- 98x IM
- 15x PM

Results:
<table>
<tr><td colspan="4">Results compared to NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>value for NM</td></tr>
<tr><td>dose-corrected trough concentration</td><td>x 1.45 (S)</td><td>x 1.34 (S)</td><td>1.45 nmol/L. mg</td></tr>
<tr><td>trough concentration</td><td>trend for an increase (p = 0.064) (NS)</td><td>NS</td><td>20.8 nmol/L</td></tr>
<tr><td>daily dose</td><td>NS</td><td>NS</td><td>15.2 mg</td></tr>
</table>

NOTE: Genotyping was performed for *3-*6, *9, *10, *41, and gene multiplication. These are the most important gene variants in this Norwegian population.
Patients with multiplied, functional alleles were excluded from the study due to few samples.</td><td>Authors' conclusion:
'This study shows that CYP-2D6 is important for the metabolism of perphenazine and zuclopenthixol.'

Dose-corrected trough concentration of zuclopenthixol versus NM:
PM: 145%
IM: 134%</td></tr>
<tr><td>ref. 2
Tveito M et al.
Impact of age</td><td>4</td><td>577 patients were treated with zuclopenthixol, 209 with oral zuclopenthixol and 368 with long-acting injectable zuclopenthixol. Routine therapeutic drug monitoring was performed. A mean of 3.2 measure-</td><td>Authors' conclusion:
'The present stu-</td></tr>
</table>

<table>
<tr>
<td>and CYP2D6 genotype on exposure of zuclopenthixol in patients using long-acting injectable versus oral formulation-an observational study including 2044 patients. Eur J Clin Pharmacol 2021;77:215-21.
PMID: 33000414.

ref. 2, continuation</td>
<td>PM: A
IM: A
UM: AA</td>
<td>ments per patient was included. Zuclopenthixol measurements below the lower limit or above the upper limit of quantification were excluded. Enzyme inducers and the most relevant CYP2D6 inhibitors (paroxetine, fluoxetine, and bupropion) were excluded.
Linear mixed model analysis, adjusting for age group (18-64 years vs. ≥ 65 years), sex, and time interval between last dose intake and sampling, was used.

CYP2D6 genotyping:
oral zuclopenthixol:
- 179x NM+gene dose 1/0
- 13x IM (only gene dose 0.25, 0.5 and 0.5/0.5)
- 15x PM
- 2x UM

long-acting injectable zuclopenthixol:
- 306x NM+gene dose 1/0
- 26x IM (only gene dose 0.25, 0.5 and 0.5/0.5)
- 22x PM
- 14x UM

Results:
<table>
<tr><td colspan="5">Geometric mean results compared to NM+gene dose 1/0:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>UM</td><td>value for NM+ gene dose 1/0</td></tr>
<tr><td colspan="5">Oral zuclopenthixol</td></tr>
<tr><td rowspan="2">dose-adjusted serum concentration</td><td>x 1.44 (S)</td><td>x 1.56 (S)</td><td>x 1.63 (trend, p = 0.092) (NS)</td><td rowspan="2">1.74 nmol/L per mg</td></tr>
<tr><td colspan="3">S for IM+PM compared to (NM+ gene dose 1/0+UM)</td></tr>
<tr><td rowspan="2">serum concentration</td><td>NS</td><td>NS</td><td>NS</td><td rowspan="2">19.4 nmol/L (range 1.0-117 nmol/L)</td></tr>
<tr><td colspan="3">NS for IM+PM compared to (NM+ gene dose 1/0+UM)</td></tr>
<tr><td rowspan="2">daily dose</td><td>NS</td><td>NS</td><td>NS</td><td rowspan="2">12.1 mg</td></tr>
<tr><td colspan="3">Trend for a decrease for IM+PM compared to (NM+ gene dose 1/0+UM) (p = 0.074) (NS)</td></tr>
<tr><td colspan="5">Long-acting injectable zuclopenthixol</td></tr>
<tr><td rowspan="2">dose-adjusted serum concentration</td><td>x 1.35 (S)</td><td>x 1.20 (S)</td><td>x 0.89 (NS)</td><td rowspan="2">2.39 nmol/L per mg</td></tr>
<tr><td colspan="3">S for IM+PM compared to (NM+ gene dose 1/0+UM)</td></tr>
<tr><td rowspan="2">serum concentration</td><td>x 1.25 (S)</td><td>NS</td><td>NS</td><td rowspan="2">22.8 nmol/L (range 2.0-109 nmol/L)</td></tr>
<tr><td colspan="3">S for IM+PM compared to (NM+ gene dose 1/0+UM)</td></tr>
<tr><td rowspan="2">daily dose</td><td>NS</td><td>NS</td><td>NS</td><td rowspan="2">10.8 mg</td></tr>
<tr><td colspan="3">NS for IM+PM compared to (NM+ gene dose 1/0+UM)</td></tr>
</table>

NOTE: Genotyping was performed for *3-*6, *9, *10, *41 and gene duplication. These are the most important gene variants in this Norwegian population.</td>
<td>dy showed that zuclopenthixol exposure increases in older patients and that the older long-acting injectable users with reduced CYP2D6 function are exposed to high serum concentrations. Also, the present study showed that similar dose reductions are required for oral and long-acting injectable users.’

Not used for dose calculation, because data were only known compared to NM+gene dose 1/0, which, based on the frequencies of variant alleles in Europe should consist for over 25% of gene dose 1/0 (IM).
In addition, for oral administration, the patient group most probably includes that of Waade 2021.</td>
</tr>
<tr>
<td>ref. 3
Patteet L et al. Genotype and co-medication dependent CYP2D6 metabolic activity: effects on serum concen-</td>
<td>4</td>
<td>6 patients were treated with zuclopenthixol. Patients were on the same oral dose for at least 7 days (n = 2; 15 and 60 mg/day) or received at least twice the same dose of long-acting subcutaneous therapy (n = 4; median 16.7 mg/day (calculated as the dose of the depot formulation divided by the number of days between two injections)). 67% of patients received more than one antipsychotic. None of the patients used a CYP2D6 inhibitor.
The authors indicate that the lack of significant results, is most probably due to the small sample size.</td>
<td>Authors’ conclusion:
‘’It was demonstrated that CYP-2D6 polymorphisms affect the serum concentrations of aripiprazole (n = 18),</td>
</tr>
</table>

<table>
<tr>
<td>trations of aripiprazole, haloperidol, risperidone, paliperidone and zuclopenthixol. Eur J Clin Pharmacol 2016;72:175-84. PubMed PMID: 26514968.

ref. 3, continuation</td>
<td>IM + gene dose 1.25-1.5: AA

UM: AA</td>
<td>Phenotype based on genotype and CYP2D6 inhibitor use:
- 2x NM (gene dose 2)
- 2x (IM + gene dose 1.25-1.5) (with a 67% chance of a patient in this group being IM based on prevalence in a larger group of patients)
- 2x UM

Results:
<table>
<tr><td colspan="4">Results compared to NM (gene dose 2):</td></tr>
<tr><td></td><td>IM + gene dose 1.25-1.5</td><td>UM</td><td>value for NM</td></tr>
<tr><td>dose-corrected C_{ss} zuclopenthixol</td><td>x 1.5 (NS)</td><td>x 0.67 (NS)</td><td>0.6 ng/ml.mg</td></tr>
<tr><td rowspan="2">zuclopenthixol dose</td><td>x 1.5</td><td>x 2.6</td><td rowspan="2">14.3 mg/day</td></tr>
<tr><td colspan="2">NS, the sample size is too small to draw accurate conclusions.</td></tr>
</table>
NOTE: Genotyping was performed for *2-*11, *15, *17, *29, *35, *41 and gene duplication. These are the most important gene variants in this Belgian population.</td>
<td>haloperidol (n = 11), risperidone (n = 20), and zuclopenthixol (n = 6), while no influence was seen on the paliperidone serum concentrations (n = 31).''

Dose-corrected C_{ss} zuclopenthixol versus gene dose 2:
IM + gene dose 1.25-1.5: 150%
UM: 67%</td>
</tr>
<tr>
<td>ref. 4
Van Berlo-van de Laar et al. Dosering aanpassen aan eliminatiesnelheid. Pharm Weekblad 2004;139:740-43.</td>
<td>4

PM: AA

IM: A</td>
<td>A total of 23 patients, 2x PM (2 mutant alleles, *3, *4 or *5), 11x IM (*1/*3, *1/*4 or *1/*5), 10x NM (*1/*1), zuclopenthixol decanoate titrated for effect (converted to daily dose: 3.6-50 mg/day), no CYP2D6 inhibitors as co-medication;

- PM: big difference between values, comparison with NM not possible. However, the trend was the same as for IM.
- IM: decrease in daily dose from 24.5 to 15 mg/day versus NM (S by 39%), increase in maximum concentration[a] from 0.77 to 1.35 mg/day (S by 75%). After 14 days, there was in increase in concentration[a] from 0.47 to 0.64 mg/day (NS by 36%). Number of changes in dose is significantly higher than for NM (3.9 versus 1.5). Similar past use of anticholinergics.</td>
<td>Authors' conclusion:
"Slower metabolism is particularly associated with higher zuclopenthixol concentrations 5 days after the dose and - to a lesser extent - with higher concentrations 14 days after the dose."
The authors recommend the following possible cautious initial dose: IMs 200 mg/2 weeks and NMs 300 mg/2 weeks

maximum concentration[a] versus NM:
IM: 175%.</td>
</tr>
<tr>
<td>ref. 5
Jaanson P et al. Maintenance therapy with zuclopenthixol decanoate: associations between plasma concentrations, neurological side effects and CYP2D6 genotype.</td>
<td>4

PM: A

IM: A</td>
<td>A total of 52 patients, 35x NM (*1/*1), 13x IM (*1/*4), 4x PM (*3/*4), zuclopenthixol decanoate 100-400 mg per 4 weeks, no CYP2D6 inhibitors as co-medication;

- PM: increase in Css[a] zuclopenthixol versus NM from 0.029 to 0.048 nM/mg (S by 66%)
- IM: increase in Css[a] from 0.029 to 0.038 nM/mg (S by 31%)
The number of mutant alleles (*3 and *4) is higher in the group with extrapyramidal disorders and tardive dyskinesia. Difference is non-significant.</td>
<td>C_{ss} versus NM:
PM: 166%
IM: 131%</td>
</tr>
</table>

Psychopharmacology 2002;162:67-73.			
ref. 6 Linnet K et al. Influence of CYP2D6 genetic polymorphism on ratios of steady-state serum concentration to dose of the neuroleptic zuclopenthixol. Ther Drug Monit 1996;18:629-34.	4 PM: A	A total of 108 patients, 12x PM (*4/*4), 107x NM + IM (64x wt/wt, 2x *1/*3, 40x *1/*4), zuclopenthixol dose 2-32 mg/day, 58 of the NM + IM used no co-medication that affects CYP2D6; - PM: increase in C_{ss}[a] zuclopenthixol versus NM + IM without co-medication from 1.25 to 2.0 nM/mg (S by 60%).	C_{ss}[a] versus NM+IM: PM: 160%
ref. 7 Jerling M et al. The CYP2D6 genotype predicts the oral clearance of the neuroleptic agents perphenazine and zuclopenthixol. Clin Pharmacol Ther 1996;59:423-8.	3 PM: A IM: A	A total of 36 patients, 20 received zuclopenthixol, of which 3x PM (*3/*3, *3/*4 or *4/*4), 9x IM (*wt/*3 or *wt/*4), 8x NM (*wt/*wt), zuclopenthixol dose 23 (1-125) mg/day, 1 PM used the CYP2D6 inhibitor levomepromazine; - PM: decrease in Cl_{or} versus NM from 95 to 42 L/hr (S by 56%). - IM: decrease in Cl_{or} versus NM from 95 to 65 L/hr (S by 32%) NOTE: unknown whether correction for dose was performed.	Cl_{or} versus NM: PM: 44% IM: 68%
ref. 8 Dahl ML et al. Disposition of the neuroleptic zuclopenthixol cosegregates with the polymorphic hydroxylation of debrisoquine in humans. Acta Psychiatr Scand 1991;84:99-102.	3 PM: A	A total of 12 healthy study subjects, 6x PM, 6x NM[#] (phenotyped with debrisoquine), a single dose of 6-10 mg zuclopenthixol, no co-medication; - PM: increase in AUC[a] versus NM from 145 to 269 nM·hr (S by 86%), decrease in Cl_{or} from 2.12 to 0.78 L/hr/kg (S by 63%), increase in t½ from 17.6 to 29.9 hours. NOTE: Phenotyping is not able to distinguish properly between NM and IM. NM[#] is therefore equal to NM+IM.	AUC[a] versus NM+IM: PM: 186%
ref. 9 SmPC Cisordinol (zuclopenthixol) 08-07-20. ao.	0 IM: A PM: A UM: A	<u>Pharmacokinetics</u>: An *in vivo* study has shown that a part of the metabolism is dependent on polymorphim in sparteine/debrisoquine oxidation (CYP2D6).	

ao.: SmPC Cisordinol Depot (zuclopenthixol decanoate) 31-08-19.
[a] corrected for the dose

Risk group	IMs with CYP2D6 inhibitor

Comments:
-

Date of literature search: 24 July 2021.

	Phenotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetic Working Group decision	PM	4 A	yes	yes	13 September 2020
	IM	4 A	yes	yes	
	UM	4 AA	yes	yes	

Mechanism:
Zuclopenthixol is primarily metabolised by CYP2D6 and to a lesser extent by CYP3A4 to inactive metabolites. A CYP2D6 genetic polymorphism may cause a change in the plasma concentration of zuclopenthixol.
The NVZA does not indicate a therapeutic range for zuclopenthixol, but in literature a therapeutic range of zuclopenthixol of 4-50 ng/ml (10-125 nmol/L) is mentioned with serum concentrations > 100 ng/ml (249 nmol/L) considered to be toxic (Hiemke C et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. Pharmacopsychiatry 2018; 51:9-62).

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+	1+
Corresponding Clinical Implication Score:		Potentially beneficial