CYP2D6: pimozide 2447/2448/2449

AUC = area under the concentration-time curve, AUEC = area under the time-effect curve, Cl_{or} = oral clearance, ΔQTc_{max} = the maximum change in the heart rate-corrected QT interval, 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, $t_{1/2}$ = half-life, UM = ultra-rapid metaboliser (gene dose $\geq$ 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:
Pimozide is primarily metabolised by CYP3A4 and CYP2D6 into inactive metabolites.
Genetic variants in CYP2D6 can result in a decreased CYP2D6 enzyme activity (intermediate metabolisers (IM)), an absent CYP2D6 enzyme activity (poor metabolisers (PM)) or an increased CYP2D6 enzyme activity (ultra-rapid metabolisers (UM)).
One study with single dosing in healthy volunteers found an decrease in pimozide clearance in patients with a decreased CYP2D6 enzyme activity (IM and PM) (Nucci 2007). Two studies, one in patients (van der Weide 2015) and one with single dosing in healthy volunteers (Desta 1999), confirmed an increase in exposure in PM, although it did not reach significance in these studies. Van der Weide 2015 found the median dose to be low (2 mg in both PM and NM), and did not find the highest trough pimozide concentration in the PM group to exceed the one in the NM group, despite at least one PM receiving a dose of 8 mg/day. However, the number of patients in this study was small. For this reason, the study does not provide enough evidence to conclude that titration of the pimozide dose in patients combined with therapeutic drug monitoring corrects for the exposure enhancing effects of the IM and PM phenotype. No significant effect of the PM phenotype on QT_c-interval was observed in Desta 1999. However, this was a small study. In addition, the risk for QT_c-interval elongation and so arrhythmias is known to increase with the concentration. Therefore, the KNMP Pharmacogenetics Working Group decided to recommend a reduced maximum pimozide dose for the PM-pimozide and IM-pimozide interactions (yes/yes-interactions).
A study found a decreased pimozide trough plasma concentration in patients with an increased CYP2D6 enzyme activity (UM), although no significant effect was found in multiple regression analysis. Based on the kinetic effect seen for IM and PM, the KNMP Pharmacogenetics Working Group concluded that a gene-drug interaction is present. The risk of an excessively high plasma concentration will not occur in UM and the literature did not contain evidence for an increase of adverse effects, like a reduced efficacy. For this reason, the KNMP Pharmacogenetics Working Group concluded that action is not needed for the UM-pimozide interaction (yes/no-interaction).
Justification of the recommended maximum doses for PM and IM
PM: The weighted mean of the dose reduction for PM, calculated based on data on clearance and exposure in a total of 15 PM, is a reduction to 55% of the standard dose (median 40%, range 27-74%). For practical reasons, this percentage was rounded off to 50%. As the risk of QT-prolongation only occurs at high doses, this means that the maximum dose for PM is equal to 50% of the maximum dose for NM. According to the Informatorium Medicamentorum, the maximum dose for adults and children of 12 years of age and older is 20 mg/day and for children of 3-12 years of age it is 0.1 mg/kg per day up to a total of 4 mg/day. This means that for PM, the maximum dose is 10 mg/ day for patients of 12 years and older, and for children younger than 12 years of age it is 0.05 mg/kg with a maximum of 2 mg/day.
The FDA recommendation is to reduce the maximum dose by a factor of 2.5 for adults and by a factor of 4 for children. The reduction for adults is similar to the reduction that we calculated. The FDA mentions for adults a maximum dose of 10 mg/day and for children a maximum dose of 0.2 mg/kg per day up to a total of 10 mg/day. The FDA therefore stipulates a maximum dose of 4 mg/day for adults and 0.05 mg/kg per day for children. This is lower than our calculated dose for adults and children of 12 years of age and older, but similar for children younger than 12 years of age.

IM: The weighted mean of the dose reduction for IM, calculated based on data on oral clearance and exposure in a total of 40 IM, is a reduction to 97% of the standard dose (median 83%, range 65-100%). To be on the safe side and because extrapolation from the weighted mean for PM suggests a required reduction to 78% of the standard dose for IM, the median value instead of the weighted mean value was used for IM. For practical reasons, the percentage of 83% was rounded off to 80%. As the risk of QT-prolongation only occurs at high doses, this means that the maximum dose for IM is equal to 80% of the maximum dose for NM. According to the Informatorium Medicamentorum, the maximum dose for adults and children of 12 years of age and older is 20 mg/day and for children of 3-12 years of age it is 0.1 mg/kg per day up to a total of 4 mg/day. This means that for IM, the maximum dose is 16 mg/day for patients of 12 years and older, and for children younger than 12 years of age it is 0.08 mg/kg with a maximum of 3.2 mg/day. The calculated dose of 3.2 mg/day is rounded off to a value that is workable in practice, namely a maximum of 3 mg/day.
The FDA has indicated that dose adjustment is not necessary for IM. However, the FDA has not indicated why it is acceptable for the plasma concentration in IM to exceed the plasma concentration for NM at the maximum dose, whilst this is not acceptable for PM.

You can find an overview of the observed kinetic and clinical consequences 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:
The Dutch Pharmacogenetics Working Group considers genotyping before starting pimozide to be potentially beneficial for the prevention of adverse events. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the Dutch Pharmacogenetics Working Group recommends adhering to the gene-drug guideline.
The clinical implication of the gene-drug interaction scores 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):
There is no direct evidence for a severe clinical effect in users of pimozide with a variant phenotype. An increased risk for QT-elongation in PM and IM was postulated based on kinetic data only. Therefore, the maximum severity code was A corresponding to CTCAE grade 0. 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 proven increase in a severe 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 Summary of Product Characteristics (SmPC) of pimozide mentions the CYP2D6 PM phenotype. At doses of 4 mg/day or higher (adult and elderly patients) or 0.05 mg/kg per day or higher (paediatric patients), the SmPC recommends to monitor the patient based on clinical status, and if applicable, to determine pimozide plasma concentrations or perform CYP2D6 genotyping. This results in the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (2 points for a recommendation to genotype).

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

Source	Code	Effect	Comments
ref. 1 van der Weide K et al. The influence of the CYP3A4*22 polymorphism and CYP-2D6 polymorphisms on serum concentrations of aripiprazole, haloperidol, pimozide, and risperidone in psychiatric patients. J Clin Psychopharmacol	3	85 patients were treated with pimozide. Therapeutic drug monitoring was routinely done. Trough plasma concentrations were determined in steady state (12 to 16 hours after dosing). For each patient, the first measured serum level and the immediate preceding daily dose were used for calculating dose-corrected plasma concentrations. Relevant co-medication was not excluded. None of the patients used CYP3A4 inhibitors. The effect of CYP3A4 inducers on dose-corrected concentrations was significant in multiple regression analysis. Parameters included in multiple regression analysis were sex, age, dose, CYP2D6 phenotype, CYP3A4*22 genotype and use of CYP3A4 inducers. Genotyping:	Authors' conclusion: 'No association between CYP2D6 status and pimozide levels was detected.'

<table>
<tr>
<td>2015;35:228-36.
PubMed PMID:
25868121
and

personal communi-cation (mean dose-corrected pimozide trough plasma concentrations)

ref. 1, continuation</td>
<td>PM: AA
IM: AA
UM: AA</td>
<td>- 40x NM
- 36x IM
- 7x PM
- 2x UM

Results:
<table>
<tr><td colspan="5">Results versus NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>UM</td><td>value for NM</td></tr>
<tr><td>dose-corrected pimozide trough plasma concentration</td><td>x 1.4 (NS)</td><td>x 1.0 (NS)</td><td>x 0.3 (S)</td><td>1.4 ng/ml. mg</td></tr>
<tr><td rowspan="3">median dose-corrected pimozide trough plasma concentration</td><td>x 2.0 (NS)</td><td>x 1.1 (NS)</td><td>x 0.4 (S)</td><td rowspan="3">1.0 ng/ml. mg</td></tr>
<tr><td colspan="3">Multiple regression analysis showed that CYP2D6 did not explain part of the variation (NS).</td></tr>
<tr><td colspan="3">The authors indicate that the absence of significance is likely to be caused by the small sample size.</td></tr>
<tr><td>median dose</td><td>x 1.0 (NS)</td><td>x 1.3 (NS)</td><td>x 1.5 (NS)</td><td>2.0 mg/day</td></tr>
<tr><td rowspan="2">highest dose</td><td>x 0.4</td><td>x 0.6</td><td>x 0.2</td><td rowspan="2">20 mg/day</td></tr>
<tr><td colspan="3">Significance not determined.</td></tr>
<tr><td rowspan="2">highest trough plasma concentration</td><td>x 0.69</td><td>x 1.2</td><td>x 0.063</td><td rowspan="2">16 ng/ml</td></tr>
<tr><td colspan="3">Significance not determined.</td></tr>
</table>
NOTE: Genotyping was performed for *3-*6, *9, *10, *41 and multiplication. These are the most important gene variants in this Dutch population.</td>
<td>Dose-corrected plasma concentration versus NM:
PM: 140%
IM: 100%
UM: 30%</td>
</tr>
<tr>
<td>ref. 2
Nucci G et al. Population pharmacokinetic modelling of pimozide and its relation to CYP2D6 genotype. Poster presented at the annual meeting of population approach group in Europe 2007.</td>
<td>3

PM: A
IM: A</td>
<td>32 healthy volunteers (2x PM, 4x IM and 26x NM) received a single dose of pimozide 2 mg. A pharmacokinetic model was created using the measured pharmacokinetics. The referen-ce does not provide any raw data.

PM versus IM versus NM:
- decrease in Cl_{or} (14.7 L/hour versus 35.8 L/hour versus 54.9 L/hour) (S)</td>
<td>Authors' conclusion: 'Our population PK results indicated that
1) CYP2D6 metabolic status impacts significantly on the PK of pimozide
2) Despite conflicting literature reports CYP2D6 appears at least as important as CYP3A4 in pimozide metabolism'

Cl_{or} versus NM:
IM: 65%
PM: 27%</td>
</tr>
<tr>
<td>ref. 3
Desta Z et al. Effect of clarithromycin on the pharmacokinetics and pharmacodynamics of pimozide in healthy poor and exten-</td>
<td>3

PM: AA</td>
<td>12 healthy volunteers (5x PM, 7x NM[#]) received a single dose of pimozide 6 mg.
Pimozide caused a significant prolongation of the QT interval during the first 20 hours.

PM versus NM[#]:
- non-significant increase in the AUC and $t_{1/2}$ by 153% and 71% respectively (NS)</td>
<td>AUC versus NM[#]:
PM: 253%</td>
</tr>
</table>

sive metabolizers of cytochrome P450 2D6 (CYP2D6). Clin Pharmacol Ther 1999;65:10-20. **ref. 3, continuation**		- non-significant increase in the oral clearance by 7.5% (NS). (Considering the effect on AUC and $t_{1/2}$, a decrease would be expected here.) - no difference in ΔQTc_{max} (NS) - non-significant increase in ΔQTc_{mean} and AUEC (0-48 hours) by 18% and 21% respectively (NS) - non-significant decrease in ΔQTc_{mean} and AUEC (0-48 hours) following inhibition of CYP3A by pre-treatment with clarithromycin by 4.6% and 4.3% respectively (NS). (Following inhibition of the most important metabolising enzyme, a stronger effect of the CYP2D6 polymorphism would be expected instead of a weaker effect.) NOTE: No genotyping, but phenotyping. Phenotyping can only distinguish between PM and the other phenotypes. Therefore, NM# is equal to NM+IM+UM.	
ref. 4 Pharmacogenetic changes to the FDA-approved Orap (pimozide) label include adult and pediatric dosing recommendations for CYP2D6 poor metabolizers. FDA-news 27-09-11.	0 PM: A	On 27 September 2011, the FDA added dose recommendations for CYP2D6 PM to the registration file of Orap (pimozide). In 2005, interaction studies demonstrated an increase in pimozide exposure by a factor 1.4 and 2.5 respectively with simultaneous use of the CYP2D6 inhibitors sertraline and paroxetine. A study using a single dose of pimozide demonstrated that CYP2D6 PM experienced a similar increase in pimozide exposure as individuals who were simultaneously taking paroxetine. Using pharmacokinetic models, the FDA calculated that the maximum dose for PM is 4 mg/day for adults and 0.05 mg/kg per day for children. For NM and IM the maximum doses are 10 mg/day for adults and 0.2 mg/kg per day for children. The registration file also included the recommendation to perform CYP2D6 genotyping for patients who require doses higher than 4 mg/day (adults) or 0.05 mg/kg per day (children). In addition, dose increases for CYP2D6 PM should not be carried out sooner than 14 days after the last increase, due to the longer time required to achieve a steady state in this patients.	
ref. 5 SmPC Orap (pimozide) 30-10-2019.	0 PM: A	<u>Dose</u>: *Poor CYP2D6 metabolism* • Adult and elderly patients: In CYP2D6 poor metabolisers, it is recommended to avoid doses higher than 4 mg/day, and to increase doses not more often than once every 14 days. • Paediatric patients: In CYP2D6 poor metabolisers, it is recommended to avoid doses higher than 0.05 mg/kg/day (with a maximum of 4 mg/day) and to increase doses not more often than once every 14 days. <u>Warning</u>: *CYP2D6 genotyping* In a clinical study, individuals with genetic variations resulting in poor CYP2D6 metabolism (approximately 5 to 10% of the population) exhibited higher pimozide concentrations than individuals with a normal CYP2D6 metabolism. The concentrations observed in poor CYP2D6 metabolisers were similar to those seen with strong CYP2D6 inhibitors such as paroxetine. The time to achieve steady state pimozide concentrations is expected to be longer (approximately 2 weeks) in poor CYP2D6 metabolisers because of the prolonged half-life. At doses of 4 mg/day or higher (adult and elderly patients) or 0.05 mg/kg/day or higher (paediatric patients), it is recommended to monitor the patient based on	

ref. 5, continuation		clinical status and, if applicable, to determine pimozide plasma concentrations or perform CYP2D6 genotyping. In addition, alternative dosing strategies are recommended in patients who are genetically CYP2D6 poor metabolisers. Interactions: Pimozide levels increased with 151% and the C_{max} with 62% upon administration of pimozide (single dose, 2 mg) to healthy volunteers treated with 60 mg paroxetine. No significant increase of the QTc-interval was observed in this study. Contra-indications: Concomitant use of CYP2D6 inhibiting drugs such as quinidine. The inhibition of this cytochrome P450 system can result in an increase in the pimozide plasma concentration and an increased risk of QT-prolongation.	
ref. 6 SPC Orap (pimozide), USA, 27-09-11.	0 PM: A	Warnings: *Drug interactions* CYP2D6 inhibitors: In healthy subjects, co-administration of pimozide 2 mg (single dose) and paroxetine 60 mg resulted in a 151% increase in pimozide AUC and a 62% increase in pimozide C_{max} compared to pimozide administered alone. The increase in pimozide AUC and C_{max} is related to the CYP2D6 inhibitory properties of paroxetine. Concomitant use of pimozide and paroxetine or other strong CYP2D6 inhibitors are contraindicated. *Pharmacogenomics* Individuals with genetic variations resulting in poor CYP2D6 metabolism (approximately 5 to 10% of the population) exhibit higher pimozide concentrations than normal CYP2D6 metabolizers. The concentrations observed in poor CYP2D6 metabolizers are similar to those seen with strong CYP2D6 inhibitors such as paroxetine. The time to achieve steady state pimozide concentrations is expected to be longer (approximately 2 weeks) in poor CYP2D6 metabolizers because of the prolonged half-life. Alternative dosing strategies are recommended in patients who are genetically poor CYP2D6 metabolizers. Dose: *Children* At doses above 0.05 mg/kg per day, CYP2D6 genotyping should be performed. In poor CYP2D6 metabolizers, Orap doses should not exceed 0.05 mg/kg/day, and doses should not be increased earlier than 14 days. *Adults* At doses above 4 mg/day, CYP2D6 genotyping should be performed. In poor CYP2D6 metabolizers, Orap doses should not exceed 4 mg/day, and doses should not be increased earlier than 14 days.	

Risk group	use of CYP2D6 inhibitors (IM), use of CYP2D6 inducers (UM) use of CYP3A4 inhibitors (IM and PM), use of CYP3A4 inducers (UM)

Comments:

- The dosing recommendation by the FDA is based on the GlaxoSmithKline study by Nucci 2007 (Rogers HL et al. CYP2D6 genotype information to guide pimozide treatment in adult and pediatric patients: basis for the U.S. Food and Drug Administration's new dosing recommendations. J Clin Psychiatry 2012;73: 1187-90). The FDA calculated the maximum allowable dose for PM in order to prevent PM reaching a higher plasma concentration than IM and NM at a dose of 10 mg/day (adults) or 0.2 mg/kg per day (children). The pharmacokinetic model demonstrated that after 30 days of use, the AUC for PM was 3.7x higher than for NM and 2.4x higher than for IM. The use of different doses in the model demonstrated that 4 mg was the maximum dose for PM, if the plasma concentrations for NM and IM are not to be exceeded at a dose of 10 mg/day.

Date of literature search: 16 July 2021.

	Phenotype	Code	Gene-drug interaction	Action	Date
Dutch Pharmacogenetics Working Group decision	PM	3 A	yes	yes	13 September 2021
	IM	3 A	yes	yes	
	UM	3 AA	yes	no	

Mechanism:
Pimozide is primarily metabolised by CYP3A4 and CYP2D6 into inactive metabolites. In addition, pimozide is also metabolised by CYP1A2.
The NVZA does not indicate a therapeutic range for pimozide, but in literature a therapeutic range of pimozide of 15-20 ng/ml is mentioned with serum concentrations > 20 ng/ml 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+	2+
Corresponding Clinical Implication Score:		Potentially beneficial