CYP2D6: propafenone 1595/1596/1597

AUC = area under the concentration-time curve, Cl_{or} = oral clearance, CTCAE = Common Terminology Criteria for Adverse Events, C_{ss} = steady state plasma concentration, HR = heart rate, HPPF = 5-hydroxypropafenone, IM = intermediate metaboliser (gene dose 0.25-1) (reduced CYP2D6 enzyme activity), MR = metabolic ratio, NM = normal metaboliser (gene dose 1.25-2.5) (normal CYP2D6 enzyme activity), NS = non-significant, PAF = paroxysmal atrial fibrillation, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), PPF = propafenone, S = significant, SmPC = Summary of Product Characteristics, UM = ultra-rapid metaboliser (gene dose ≥ 2.75) (elevated 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 healthcare professional should consider the next best option.

Brief summary and justification of choices:
Propafenone is converted by CYP2D6 to the active metabolite 5-hydroxypropafenone. It is converted by CYP1A2 and CYP3A4 to N-depropylpropafenone, which is less active. Propafenone is a CYP2D6 inhibitor. Propafenone pharmacokinetics for phenotypes other than PM are therefore non-linear (a 3-fold increase in a 300 mg/day dose leads to a 10-fold increase in propafenone concentration).
CYP2D6 gene variants influence propafenone and 5-hydroxypropafenone plasma concentrations and the sum of both (Mörike 2008 (including 4 PM, 4 IM, and 3 UM+NM (gene dose 2.5-3)), Chen 2003 (8 IM), Cai 2002 (7 IM), Chow 2001 (9 PM), Siddoway 1987 (6 PM), Cai 2001 (5 healthy IM), Labbe 2000 (7 healthy PM), Lee 1990 (5 healthy PM), and the SmPCs of propafenone). A study in children and young adults, including 20 with genetically reduced CYP2D6 enzyme activity (intermediate metabolisers (IM), 4 with absent CYP2D6 activity (poor metabolisers (PM)), and 2 with genetically elevated CYP2D6 activity (1 ultra-rapid metaboliser (UM) and one with gene dose 2.5), showed the percentage of patients with systemic adverse events, the percentage of patients with discontinuation due to systemic adverse events, and the total number of adverse events per patient to decrease with increasing CYP2D6 activity (Sunthankar 2022). Another study showed that the incidence of central side effects was increased in the 6 PM patients (Siddoway 1987). In addition, an IM and a PM case with adverse events were reported (Doki 2020 and Mörike 1995). A study of propafenone showed that it was ineffective as prophylactic treatment for paroxysmal atrial fibrillation in the 5 UM patients (Jazwinska-Tarnawska 2001).
Based on this, the KNMP Pharmacogenetics Working Group concluded that there is a gene-drug interaction and that action is needed for all aberrant phenotypes (yes/yes-interactions).
An overview of the observed clinical and kinetic effects per phenotype is provided in the background information text of the gene-drug interactions in the KNMP Kennisbank. You may also have access to this background information text via your pharmacy or physician electronic decision support system. Justification for the recommendation for each phenotype is provided below.
Justification of recommendations
The calculation of the dose adjustment was made on the basis of the sum of propafenone and 5-hydroxypropafenone, which is at least as potent as propafenone. The metabolite 5-desalkylpropafenone is also active, but to a lesser extent and was therefore left out of consideration.

PM: Based on five studies with a total of 32 PM (Chow 2001, Labbe 2000, Dilger 1999, Lee 1990, and Siddoway 1987, the weighted mean of the dose adjustment is a reduction to 30% of the normal dose (23%-44%; median 26%). Propafenone has a narrow therapeutic range and dose adjustments should therefore be accompanied by ECGs and plasma concentration monitoring. Each method on its own provides insufficient information.

IM: It is not possible to offer adequately substantiated recommendations for dose reduction based on the literature. There are no data on the sum of propafenone and 5-hydroxypropafenone for IM patients.
Propafenone has a narrow therapeutic range and the dose should therefore preferably be guided by side effects and ECG while plasma concentrations are monitored. Each method on its own provides insufficient information.
Another possibility is to choose an alternative.

UM: It is not possible to offer adequately substantiated recommendations for dose increase based on the literature. The normal dose may be ineffective. Choose an alternative as a precaution or monitor plasma concentrations and ECG.

Antiarrhythmic drugs hardly if at all metabolised by CYP2D6 include sotalol, disopyramide, quinidine and amiodarone.

Recommendation concerning pre-emptive genotyping, including justification of choices:

The KNMP Pharmacogenetics Working Group considers genotyping before starting propafenone to be potentially beneficial for the prevention of side effects and drug 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):

Only one publication reports a severe clinical effect (severity code ≥ D, corresponding to CTCAE grade ≥ 3): Jazwinska-Tarnawska 2001 found propafenone to be ineffective as prophylaxis for paroxysmal atrial fibrillation in 5 UM patients. However, these patients were phenotypically UM. They were not genotyped. This indicates that it cannot be excluded that (part of) these patients were actually NM with a high CYP2D6 activity. In addition, another study with 3 UM+NM (gene dose 2.5-3) did not find a difference in effectiveness as prophylaxis of atrial tachyarrythmia between these patients and NM with gene dose ≤ 2 (effectiveness in 67% versus 69% of patients) (Mörike 2008). In addition, a third study in children and young adults with 1 UM and 1 patient with gene dose 2.5 did not find an effect of CYP2D6 gene dose on the percentage of patients in whom therapy was discontinued due to ineffectiveness (Sunthankar 2022). For this reason, the KNMP Pharmacogenetics Working Group concluded that the severe clinical effect observed in Jazwinska-Tarnawska 2001 is too uncertain to base a genotyping recommendation on it, and so to include it in the Clinical Implication Score. Ignoring the severe clinical effect found in this study results in a score of 0 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 at least one (not ignored) publication with a severe clinical effect (grade ≥ 3)).

Ignoring this study also results in the absence of studies showing an increase in severe clinical effects in patients with a CYP2D6 gene variant. This results in a score of 0 of the maximum of 3 points for both the second and third criterion of the clinical implication score: the level of evidence supporting an associated clinical effect grade ≥ 3 (only points for at least one (not ignored) study showing an association with a clinical effect grade ≥ 3) and the number needed to genotype (NNG) in the Dutch population to prevent one clinical effect code ≥ D (grade ≥ 3) (only points for NNG < 1000).

The Summary of Product Characteristics (SmPC) Rytmonorm (propafenone) 19-07-21 mentions PM to have a longer elimination half-life than NM, but does not recommend to genotype nor mentions any CYP2D6 phenotype as a contra-indication. 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 no recommendation to genotype and no genotype/phenotype mentioned as a contra-indication).

The table below uses the KNMP definitions for NM, PM, IM and UM. As a result, the definitions for NM, PM, IM and UM in the table below can differ from the definitions used by the authors in the articles.

Source	Code	Effect	Comments
ref. 1 Sunthankar SD et al. Influence of CYP2D6 genetic variation on adverse events with propafenone in the pediatric and young adult population. Clin Transl Sci 2022 May 5 [online ahead of print]. PMID: 35514162.	4	Data from a biobank coupled to an electronic health record database were analysed for 69 paediatric and young adult patients (median age 0.3 years (range 0-26 years)) treated with propafenone (median initial and maximum dose 235 and 250 mg/m^2 per day, respectively). Reason for propafenone discontinuation was categorized as refractory arrhythmia, intolerance of propafenone adverse events, completion of therapy following ablation or spontaneous resolution of arrhythmia, and patient non-adherence. ECG changes defined as adverse events included atrioventricular nodal block, prolongation of QRS or QTc intervals, and bradycardia. Designation of prolonged QRS or QTc interval was determined by clinical documentation of the attending physician as there are no clear definitions in the literature for prolonged QRS or QTc while on propafenone. In patients who underwent heart surgery and required propafenone in the postoperative period,	Authors' conclusion: 'Awareness of CYP2D6 activity score and patient age may aid in determining an individual's risk for an adverse event with propafenone administration.'

<table>
<tr>
<td>ref. 1, continuation</td>
<td>PM: C
IM: C
UM: AA#</td>
<td>
ECG changes that occurred intraoperatively or within 24 h post-operatively were not attributed to propafenone adverse events.
Gastrointestinal adverse events were defined as dysgeusia and gastrointestinal intolerance, which encompassed increased secretions, gagging, decreased appetite, or poor feeding. In neonates and infants, it can be difficult to discern if increased secretions and gagging are due to drug adverse events or normal new-born behaviour; therefore, these were included as adverse events only if it was a clear change from baseline, led to poor weight gain, or was documented as the reason for medication discontinuation, with resolution after drug discontinuation.
Neurologic side effects were defined as dizziness, headaches, flushing, fatigue, and irritability.
Systemic adverse events encompassed hypotension, neurologic adverse events, and gastrointestinal adverse events.
Relevant co-medication was not excluded. 30% of patients used a CYP2D6 inhibitor concomitantly and 3% a CYP2D6 inducer. However, there was no association between the presence of a CYP2D6 inhibitor or inducer and adverse events, and correcting for the use of CYP2D6 inhibitors or inducers did not significantly affect the results for the percentage of patients with any adverse event.
Multiple and linear regression analysis was used to investigate the presence of an association between CYP2D6 activity scores and propafenone adverse events.

Genotyping:
- 43x NM
- 20x IM
- 4x PM
- 2x UM+gene dose 2.5 (1x UM, 1x gene dose 2.5)

Results:
<table>
<tr><td colspan="5">Results compared to NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>UM + gene dose 2.5</td><td>value for NM</td></tr>
<tr><td rowspan="2">% of patients with any adverse event</td><td>x 1.5</td><td>x 1.5</td><td>x 0.0</td><td>33%</td></tr>
<tr><td colspan="4">trend for a decrease with increasing CYP-2D6 activity score (p = 0.055) (NS)

Results were not significantly different in multivariable analysis correcting for age, maximum propafenone dose indexed for body surface area, and use of CYP2D6 inhibitors or inducers.</td></tr>
<tr><td rowspan="2">% of patients with ECG adverse events</td><td>x 0.98</td><td>x 1.2</td><td>x 0.0</td><td>26%</td></tr>
<tr><td colspan="4">NS for the comparison between CYP2D6 activity scores.</td></tr>
<tr><td>average PR, QRS, and QTc intervals</td><td colspan="4">NS for the comparison between CYP2D6 activity scores (determined by linear regression).</td></tr>
<tr><td rowspan="2">% of patients with systemic adverse events</td><td>x 2.2</td><td>x 2.6</td><td>x 0.0</td><td>12%</td></tr>
<tr><td colspan="4">OR = 0.33 (95% CI: 0.13-0.88) (S) with increasing CYP2D6 activity score</td></tr>
<tr><td rowspan="2">% of patients with discontinuation due to adverse events</td><td>x 1.3</td><td>x 1.3</td><td>x 0.0</td><td>19%</td></tr>
<tr><td colspan="4">trend for a decrease with increasing CYP-2D6 activity score (p = 0.094) (NS)</td></tr>
<tr><td>% of patients with discontinuation due to systemic adverse</td><td colspan="4">OR = 0.28 (95% CI: 0.09-0.83) (S) with increasing CYP2D6 activity score</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

<table>
<tr>
<td>ref. 1, continuation</td>
<td></td>
<td>
<table>
<tr><td>events</td><td></td></tr>
<tr><td>total number of adverse events per patient</td><td>β1 = -0.31 (95% CI: -0.60 – -0.03) (S) with increasing CYP2D6 activity score (determined by linear regression)</td></tr>
<tr><td>% of patients with discontinuation due to drug inefficacy</td><td>NS for the comparison between CYP2D6 activity scores</td></tr>
</table>

Genotyping was for *2 through *7, *9, *10, *17, *29, *41, and gene multiplication. These are the most important variants in this population from the USA.
</td>
<td></td>
</tr>
<tr>
<td>ref. 2
Doki K et al. Effect of CYP2D6 genetic polymorphism on peak propafenone concentration: no significant effect of CYP2D6*10. Pharmacogenomics 2020;21:1279-88.
PMID: 33203295.</td>
<td>1

IM: C</td>
<td>Propafenone dosing was discontinued in a 76-year old woman due to presentation with sick sinus syndrome as an adverse event. The propafenone daily dose in this woman did not exceed 450 mg/day (either 225, 300 or 450 mg/day, but which of the three was not mentioned). The peak propafenone concentration was 1241 ng/ml, while the mean peak propafenone concentration in 15 NM on a dose of 225-450 mg/day was 238 ng/ml. The woman was CYP2D6*1/*5.
The women did not use any strong CYP2D6 inhibitors, but it was not reported whether the women used the weak CYP2D6 inhibitor carvedilol. The women had normal hepatic function, but it was not reported whether she had normal or impaired renal function. In 66 patients, no effect of age and female sex on propafenone clearance was found.</td>
<td>Authors’ conclusion:
‘As indicated in a case with an adverse event, CYP2D6 PM allele carriers have the potential to reach a toxic peak propafenone concentration..’</td>
</tr>
<tr>
<td>ref. 3
Mörike K et al. Propafenone for the prevention of atrial tachyarrhythmias after cardiac surgery: a randomized, double-blind placebo-controlled trial.
Clin Pharmacol Ther 2008;84:104-10.</td>
<td>3

PM: A</td>
<td>37 patients after heart surgery, 4x PM (gene dose 0), 4x IM (gene dose 0.25-1 (1 or 2 alleles with gene dose 0.25 or 0.5)), 26x NM+IM (gene dose 1 (fully functional with non-functional allele) or 1.25-2), 3x UM+NM (gene dose 2.5-3), received propafenone for 1 week (1 mg/kg IV (intravenous) in 1 hour, followed by 4 mg/kg per 24 hours IV until the next morning, followed by 150 mg 3 times daily oral). 25 patients, 4x IM, 20x NM+IM, 1x UM+NM (gene dose 3), started using propafenone, but stopped early due to side effects. Co-medication with CYP2D6 inhibitors and anti-arrhythmic drugs were excluded, but co-medication with beta-blockers was not. Endpoint arrhythmia was atrial tachyarrhythmia for ≥ 30 seconds.

Cardiac side effects:
- There were no major differences in the distribution of phenotypes in the group that discontinued the study due to side effects and the group that completed the study. The percentage of patients who discontinued due to side effects was not much lower in the placebo group (18.9% versus 13.3%).
- no difference in the extent of the temporary increase in heart rate and the increase in PR interval after propafenone infusion between the different CYP2D6 phenotypes.

(NM+IM) + (UM+NM):
- non-significant difference in the incidence of endpoint arrhythmia versus IM + PM (NS, from 25.0% to 31.0%), despite a ~19-fold lower C_{ss}.
- no difference in plasma concentration at the end of the IV administration between patients with and without endpoint arrhythmia (214.8 and 213.0 ng/mL respectively).

PM versus (NM+IM):
- trough concentration 2 days after initiation of oral propafenone increased by 1967% (S for the trend PM, IM, NM+IM, UM+NM; from 54.9 to 1135 ng/mL).
- incidence of endpoint arrhythmia increased by 63% (NS,</td>
<td>Authors’ conclusion:
‘Plasma propafenone concentrations were markedly influenced by CYP2D6 genotype-derived phenotype.’
‘It would appear that the CYP2D6 polymorphism has little impact on the tolerability of propafenone when the dosage does not exceed 600 mg/day.’</td>
</tr>
</table>

ref. 3, continuation	IM: A UM: A	from 31% to 50%). IM versus (NM+IM): - trough concentration 2 days after initiation of oral propafenone increased by 1324% (S for the trend PM, IM, NM, UM; from 54.9 to 782 ng/mL). - incidence of endpoint arrhythmia decreased (NS, from 31% to 0%). (UM+NM) versus (NM+IM): - trough concentration 2 days after initiation of oral propafenone decreased by 61% (S for the trend PM, IM, NM, UM; from 54.9 to 21.2 ng/mL). - clearance increased by 5% (NS, from 14.9 to 15.7 mL/min per kg). - no difference in incidence of endpoint arrhythmia (NS, from 31% to 33%). Genotyping was for *3 through *10, *41, and gene duplication. These are the most important variants in this German population.	C_{ss} versus NM+IM: PM: 2067% IM: 1424% UM+NM: 39%
ref. 4 Chen B et al. Influence of CYP2D6*10B genotype on pharmacokinetics of propafenone enantiomers in Chinese subjects. Acta Pharmacol Sin 2003;24:1277-80.	3 IM: A	17 healthy volunteers, 8x *10/*10, 5x *1/*10 and 4x *1/*1, a single dose of 400 mg propafenone, no co-medication; - *10/*10: *S*-PPF and *R*-PPF AUC increased from 1534 and 1136 to 3172 and 2277 μg/L·h respectively versus *1/*1 (S by 107% and 100%). *S*-PPF AUC was 40% higher than *R*-PPF (S) - *1/*10: *S*-PPF and *R*-PPF AUC increased from 1534 and 1136 to 1891 and 1467 μg/L·h respectively versus *1/*1 (NS by 23% and 29%). *S*-PPF AUC was 29% higher than *R*-PPF (S) - *1/*1: *S*-PPF AUC was 35% higher than *R*-PPF (S) The *S*-PPF/*R*-PPF ratio was no different among the 3 genotype groups.	*S*-PPF+*R*-PPF AUC versus 1/*1: IM: 207%
ref. 5 Cai WM et al. Effect of CYP-2D6*10 genotype on propafenone pharmacodynamics in Chinese patients with ventricular arrhythmia. Acta Pharmacol Sin 2002;23:1040-4.	2 IM: A	17 patients with ventricular arrhythmia, 7x *10/*10, 7x *1/*10, 3x *1/*1, 4x propafenone 600 mg/day and 13x (6x *10/*10, 4x *1/*10 and 3x *1/*1) propafenone 450 mg/day for 7 days, no cardiac medication, other co-medication not known; *kinetic endpoints* - *10/*10: C_{max} increased from 125 to 233 μg/L versus *1/*1 (S by 87%) - *1/*10: C_{max} **decreased** from 125 to 75 μg/L versus *1/*1 (S by 40%) *clinical endpoints* - *10/*10: stronger decrease in premature ventricular contractions versus *1/*1 (S by 66%). Change in HR, PR interval and QRS interval was non-significantly different from *1/*1. - *1/*10: premature ventricular contractions, HR, PR interval and QRS interval were non-significantly different from *1/*1.	Authors' conclusion: 'Elevated plasma concentration is consistent with better efficacy of propafenone in patients with ventricular arrhythmia.'
ref. 6 Cai WM et al. Simultaneous modeling of pharmacokinetics and pharmacodynamics of propafenone in healthy subjects. Acta Pharmacol Sin 2001;22:956-60.	3 IM: A	10 healthy volunteers, 5x IM and 5x NM# (phenotyped), a single dose of 400 mg propafenone, no co-medication; - IM: propafenone AUC increased from 2948 to 5126 μg·h/L versus NM (S by 74%). NOTE: genotype not known.	Phenotyping described in Cai et al. Acta Pharmacol Sin 1997. AUC versus NM#: IM: 174%

ref. 7 Jazwinska-Tarnawska E et al. The influence of CYP2D6 polymorphism on the antiarrhythmic efficacy of propafenone in patients with paroxysmal atrial fibrillation during 3 months propafenone prophylactic treatment. Int J Clin Pharmacol Ther 2001;39:288-92.	3 PM: A UM: D	42 patients with PAF, 11x PM, 26x NM + IM, 5x UM (phenotyped using sparteine), propafenone 300-450 mg/day for 3 months, co-medication not known; - PM: propafenone is effective as PAF prophylaxis in 100% of patients. - UM: propafenone is effective as PAF prophylaxis in 0% of patients. Study discontinued in the first week due to occurrence of atrial fibrillation. - NM: propafenone is effective as PAF prophylaxis in 61% of patients. There was a significant correlation between phenotype and ability to maintain sinus rhythm. NOTE: genotype not known.	Authors' conclusion: 'Antiarrhythmic efficacy of propafenone in patients with paroxysmal atrial fibrillation is associated with oxidation phenotype.'
ref. 8 Chow MS et al. Evaluation of CYP2D6 oxidation of dextromethorphan and propafenone in a Chinese population with atrial fibrillation. J Clin Pharmacol 2001;41:92-6.	4 PM: A	60 patients with PAF, 9x PM, 51x NM# (phenotyped using dextromethorphan); 38 patients (8x PM) received propafenone 150 mg 2-3 times daily for 1-8 weeks, no co-medication; - PM: propafenone C_{ss} increased from 129 to 486 ng/mL versus NM (S by 277%), HPPF C_{ss} decreased from 109 to 63 ng/mL (NS by 42%). NOTE: genotype not known.	PPF+HPPF C_{ss} versus NM#: PM: 310%
ref. 9 Labbe L et al. Pharmacokinetic and pharmacodynamic interaction between mexiletine and propafenone in human beings. Clin Pharmacol Ther 2000;68:44-57.	4 PM: A	15 healthy volunteers, 7x PM (6x *4/*4, 1x *4/*5) and 8x NM + IM (6x *1/*1, 1x *1/*4, 1x genotype not known), (phenotyped using dextromethorphan or debrisoquine, screened for alleles *3 to *7), propafenone 150 mg twice daily for 7 days, no co-medication; *kinetic endpoints* - PM: PPF $AUC_{0\text{-}12h}$ increased from 2.0 to 14 mM·h versus NM + IM (S by 600%). HPPF $AUC_{0\text{-}12h}$ decreased from 1.2 to 0.2 mM·h (S by 83%). *clinical endpoints* Of the ECG parameters QRS, QTc, RR and PR intervals, the only parameter that differed significantly between PM and NM+IM was the PR interval.	PPF+HPPF AUC versus NM + IM (*1/*1+*1/*4): PM: 444%
ref. 10 Dilger K et al. Consequences of rifampicin treatment on propafenone disposition in extensive and poor metabolizers of CYP2D6. Pharmacogenetics 1999;9:551-9.	4 PM: AA	12 healthy volunteers, 6x PM and 6x NM# (phenotyped and genotyped, data not reported), 140 mg propafenone IV and 300 mg oral propafenone 2 hours later, no co-medication; *kinetic endpoints* - PM: HPPF below the limit of detection. Propafenone AUC_{IV} increased from 10.21 to 31.72 mM·h versus NM# (by 211%) AUC_{oral} from 6.86 to 54.30 (by 692%). Significances not reported. *clinical endpoints* - PM: 140 mg propafenone IV led to less QRS prolongation versus NM#, from 10.6% to 8.2% (by 23%). 300 mg oral propafenone led to a decrease from 21.3 to 14.6% (by 32%). NOTE: genotype not known.	PPF+HPPF AUC_{IV} versus NM#: PM: 288% PPF+HPPF AUC_{oral} versus NM#: PM: 527%
ref. 11 Cai WM et al.	3	17 healthy volunteers, 1x PM and 16x NM# (phenotyped using dextromethorphan), a single dose of 400 mg propafenone, no co-	

The influence of CYP2D6 activity on the kinetics of propafenone enantiomers in Chinese subjects. Br J Clin Pharmacol 1999;47:553-6.	PM: AA	medication; *kinetic endpoints* - PM: AUC and C_{max} were 2-3x higher than in NM[#] (NS). - NM[#]: *S*-PPF AUC was 35% higher than *R*-PPF AUC (S), no difference in t½ and C_{max} between the enantiomers *clinical endpoints* side effects in 4x NM[#] (dizziness) and 1x PM (dizziness + gastrointestinal disorders) NOTE: genotype not known.	
ref. 12 Mörike K et al. Propafenone in a usual dose produces severe side-effects: the impact of genetically determined metabolic status on drug therapy. J Intern Med 1995;238:469-72.	2 PM: C	72-year-old patient hospitalised due to dizziness and head injury as a result of a fall and bradycardia. The patient had been using propafenone 150 mg 3 times daily and various co-medications for dizziness for 18 months. Plasma concentrations: propafenone 1565 ng/mL (central side effects such as dizziness are said to occur > 900 ng/mL), 5-hydroxypropafenone < 10 ng/mL, N-desalkylpropafenone 254 ng/mL. Phenotyped and genotyped, patient was PM (MR sparteine was 84, *4/*4 or *4/*5). Dizziness disappeared after discontinuation of propafenone.	Authors' comment: 'It is unclear why the symptoms in this patient occurred so unexpectedly late after initiation of propafenone therapy.' Antiarrhythmic drug-induced cardiac arrhythmia is known to occur also after prolonged use. The immediate cause is not always known.
ref. 13 Mörike KE et al. Quinidine-enhanced beta-blockade during treatment with propafenone in extensive metabolizer human subjects. Clin Pharmacol Ther 1994;55:28-34.	4 PM: AA	9 healthy volunteers, 2x PM and 7x NM[#] (phenotyped using debrisoquine), 225 mg propafenone 3 times daily for 7 days, no co-medication; - PM: greater reduction in heart rate than in NM[#], 10% and 6.1% respectively (NS by 64%) NOTE: genotype not known.	
ref. 14 Lee JT et al. The role of genetically determined polymorphic drug metabolism in the beta-blockade produced by propafenone. N Engl J Med 1990;21:1764-8.	4 PM: A	14 healthy volunteers, 5x PM and 9x NM[#] (13x phenotyped using debrisoquine, 1x using propafenone), propafenone 150, 225 or 300 mg 3 times daily, no co-medication; Results for 150 mg 3 times daily dose: *kinetic endpoints* - PM: propafenone C_{ss} increased from 0.56 to 3.18 µM versus NM[#] (S by 468%), N-desalkyl PPF C_{ss} increased from 0.07 to 0.26 µM (S by 271%), HPPF was below the detection limit in PM patients. *clinical endpoints* - PM: a significantly higher isoproterenol dose was needed to increase the heart rate by 25 BPM and to reduce the heart rate by 10% during exercise. NOTE: 2 PM patients discontinued the study due to the side effect severe nausea. NOTE: genotype not known.	PPF+HPPF C_{ss} versus NM[#]: - 150 mg 3 times daily dose: PM: 383% - 225 mg 3 times daily dose: PM: 306% - 300 mg 3 times daily dose: PM: 180%

ref. 15 Siddoway LA et al. Polymorphism of propafenone metabolism and disposition in man: clinical and pharmacokinetic consequences. Circulation 1987;75:785-91.	4 PM: B	28 patients with ventricular arrhythmia, 6x PM and 22x NM# (phenotyped using debrisoquine), dose titration from 300 mg twice daily to 300 mg 3 times daily, no antiarrhythmic drugs, beta-blockers or CYP inhibitors as co-medication; *kinetic endpoints* - PM: propafenone C_{ss}[a] increased from 1.1 to 2.5 ng/mL/mg versus NM# (S by 130%), Cl_{or} decreased from 1115 to 264 mL/min (S by 76%), t½ is ~72 hours. HPPF below the limit of detection. *clinical endpoints* - PM: no significant difference in antiarrhythmic effect (67%), effective dose or ECG alterations versus NM#. The C_{ss} at which ectopic ventricular depolarisation in responders was reduced by more than 70% was 373% higher than in NM# (S). Central side effects increased from 14 to 67% (S by 379%). NOTE: genotype not known.	Authors' conclusion: 'Based on our results in this relatively small group of patients, we conclude that metabolic phenotype is important in the toxicity of propafenone, but its importance with respect to the electrophysiologic effects of the drug is unclear.' PFF + HPFF C_{ss} versus NM#: PM: 227%
ref. 16 SmPC Rytmonorm (propafenone) 19-07-21.	0 PM: A	<u>Pharmacokinetic properties</u> There are two genetically determined patterns of propafenone metabolism. In over 90% of patients, the drug is rapidly and fully metabolised with an elimination half-life of 2 to 10 hours (these patients are normal metabolisers). These patients metabolise propafenone into two active metabolites: 5-hydroxypropafenone, which is formed by CYP2D6, and N-depropylpropafenone (norpropafenone) which is formed by both CYP3A4 and CYP1A2. In less than 10% of patients, metabolism of propafenone is slower because the 5-hydroxy metabolite is not formed or is minimally formed (these patients are poor metabolisers). The estimated immediate-release propafenone elimination half-life ranges from two to ten hours in normal metabolisers and from ten to 32 hours in poor metabolisers. In normal metabolisers, saturation of the hydroxylation pathway (CYP2D6) results in non-linear pharmacokinetics. In poor metabolisers, propafenone pharmacokinetics is linear.	
ref. 17 SmPC Rythmol SR (propafenone), USA, 02-11-18.	0 PM: A	<u>Dose</u>: The combination of cytochrome P450 3A4 (CYP3A4) inhibition and either cytochrome P450 2D6 (CYP2D6) deficiency or CYP-2D6 inhibition with the simultaneous administration of propafenone may significantly increase the concentration of propafenone and thereby increase the risk of proarrhythmia and other adverse events. <u>Warning:</u> *Drug interactions: simultaneous use with inhibitors of cytochrome P450 isoenzymes 2D6 and 3A4* Propafenone is metabolized by CYP2D6, CYP3A4, and CYP1A2 isoenzymes. Approximately 6% of Caucasians in the U.S. population are naturally deficient in CYP2D6 activity and other demographic groups are deficient to a somewhat lesser extent. Increased exposure to propafenone may lead to cardiac arrhythmias and exaggerated beta-adrenergic blocking activity. Because of its metabolism, the combination of CYP3A4 inhibition and either CYP2D6 deficiency or CYP2D6 inhibition in users of propafenone is potentially hazardous. <u>Drug interactions</u>: The combination of CYP3A4 inhibition and either CYP2D6 deficiency or CYP2D6 inhibition with administration of propafenone may increase the risk of adverse reactions, including proarrhythmia. Concomitant administration of quinidine (50 mg 3 times daily) with 150-mg immediate-release propafenone 3 times daily	

ref. 17, continuation		decreased the clearance of propafenone by 60% in normal metabolizers, making them poor metabolizers. Steady-state plasma concentrations increased by more than 2-fold for propafenone and decreased 50% for 5-OH-propafenone. Pharmacokinetics: There are 2 genetically determined patterns of propafenone metabolism. In over 90% of patients, the drug is rapidly and extensively metabolized with an elimination half-life from 2 to 10 hours. These patients metabolize propafenone into 2 active metabolites: 5-hydroxypropafenone, which is formed by CYP2D6, and N-depropylpropafenone (norpropafenone) which is formed by both CYP3A4 and CYP1A2. In less than 10% of patients, metabolism of propafenone is slower because the 5-hydroxy metabolite is not formed or is minimally formed. In these patients, the estimated propafenone elimination half-life ranges from 10 to 32 hours. Decreased ability to form the 5-hydroxy metabolite of propafenone is associated with a diminished ability to metabolize debrisoquine and a variety of other drugs, such as encainide, metoprolol, and dextromethorphan, whose metabolism is mediated by the CYP2D6 isozyme. As a consequence of the observed differences in metabolism, administration of Rythmol SR to slow and normal metabolizers results in significant differences in plasma concentrations of propafenone, with slow metabolizers achieving concentrations about twice those of the normal metabolizers at daily doses of 850 mg/day. At low doses the differences are greater, with slow metabolizers attaining concentrations about 3 to 4 times higher than normal metabolizers. In normal metabolizers, saturation of the hydroxylation pathway (CYP2D6) results in greater-than-linear increases in plasma levels following administration of Rythmol SR capsules. In slow metabolizers, propafenone pharmacokinetics is linear. Because the difference decreases at high doses and is mitigated by the lack of the active 5-hydroxy metabolite in the slow metabolizers, and because steady-state conditions are achieved after 4 to 5 days of dosing in all patients, the recommended dosing regimen is the same for all patients. The larger inter-subject variability in blood levels requires that the dose of the drug be titrated carefully in patients with close attention paid to clinical and ECG evidence of toxicity. Inter-subject variability of pharmacokinetics appears to be substantially less in the poor-metabolizer group than in the normal-metabolizer group, suggesting that a large portion of the variability is intrinsic to CYP2D6 polymorphism rather than to the formulation. *In vitro* and *in vivo* studies have shown that the R-isomer of propafenone is cleared faster than the S-isomer via the 5-hydroxylation pathway (CYP2D6). This results in a higher ratio of S-propafenone to R-propafenone at steady state. Both enantiomers have equivalent potency to block sodium channels; however, the S-enantiomer is a more potent beta-antagonist than the R-enantiomer. Following administration of Rythmol immediate-release tablets or Rythmol SR capsules, the S/R ratio for the area under the plasma concentration-time curve was about 1.7. The S/R ratios of propafenone obtained after administration of 225-mg, 325-mg, and 425-mg Rythmol SR are independent of dose. In addition, no difference in the average values of the S/R ratios is evident between genotypes or over time.	

[a] = corrected for dose

NM[#]: Phenotyping cannot distinguish between NM, IM and UM. NM[#] is therefore equal to NM + IM + UM.

Risk group	IM patients with CYP2D6 inhibitors

Comments:

- For the period after 2008, kinetic studies were only included if the clearance or (dose-corrected) exposure was determined per aberrant phenotype and compared to those in NM or in patients with gene dose 2 (the main NM group in European patients).
  For this reason, Doki K et al. Effect of CYP2D6 genetic polymorphism on peak propafenone concentration: no significant effect of CYP2D6*10. Pharmacogenomics 2020;21:1279-88. PMID: 33203295 was only included as a case report. This study determined peak plasma concentrations that were not corrected for the daily dose in patients receiving 150 mg propafenone 2 or 3 times daily. In addition, data were only determined for IM+PM and not for PM and the most prevalent IM in the European population (gene dose 1) separately.

Date of literature search: 31 May 2022

	Phenotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	PM	4 C	yes	yes	12 September 2022
	IM	4 C	yes	yes	
	UM	4 D	yes	yes	

Mechanism:

Propafenone is metabolised by CYP2D6 to the active metabolite 5-hydroxypropafenone. It is converted by CYP1A2 and CYP3A4 to N-depropylpropafenone, which is less active.
Propafenone is a CYP2D6 inhibitor. Propafenone pharmacokinetics for phenotypes other than PM are therefore non-linear (a 3-fold increase in a 300 mg/day dose leads to a 10-fold increase in propafenone concentration).

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