CYP2D6: flecainide 1592/1593/1594

AUC = area under the concentration-time curve, Cl_{or} = oral clearance, CTCAE = Common Terminology Criteria for Adverse Events, 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, 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) (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:
Flecainide is primarily converted by CYP2D6 to inactive metabolites. Flecainide has a relatively narrow therapeutic range (plasma concentration 200-1000 ng/mL).
Some studies found a significant increase in the plasma concentration of flecainide for patients with reduced CYP-2D6 activity (IM and PM) (Doki 2006, Gross 1991, Gross 1989, and Mikus 1989). A patient with a PM genotype in combination with reduced renal function died due to flecainide toxicity following use of flecainide 100 mg/day (Palmiere 2012). A preterm neonate with an IM genotype developed heart block with widened QRS complex after using oral flecainide 2 mg/kg twice daily (Poh 2020). In addition, the response to a flecainide provocation test always occurs within 30 minutes for IM (Calvo 2015). However, this earlier response cannot be readily explained by the slower clearance in IM, because response is dependent on the flecainide peak concentration and administration was by continuous infusion. There are no studies into the kinetic and clinical consequences for UM. Standard dosing may be ineffective for UM.
Although there is only limited evidence for clinical consequences of the gene-drug interaction, action is nevertheless recommended for all three genotype groups (yes/yes-interactions), considering the relatively narrow therapeutic range. Monitoring of the plasma concentration and the ECG is recommended for UM, or an alternative should be selected. Examples of anti-arrhythmic drugs that are not metabolised by CYP2D6 (or to a lesser extent) include sotalol, disopyramide, quinidine and amiodarone. A dose reduction in combination with monitoring is recommended for PM and IM.
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. A justification of the dose recommendation for PM and IM is provided below.
Justification of dose recommendation
Dose adjustments have been calculated on the basis of the AUC or C_{ss} of flecainide.
If the effect is only known versus NM + IM + UM (as is the case in Mikus 1989 and Gross 1991), then it is assumed – given the much higher prevalence of NM – that NM + IM + UM is approximately equal to NM.
If possible, the difference in AUC or C_{ss} was calculated relative to gene dose 2 instead of relative to NM (gene dose 2 + gene dose 1.25-1.5) for Asian studies. The reason for this is that most European NMs have gene dose 2. The frequency of gene dose 1.25-1.5 is very low here.

PM: Based on three studies with a total of 15 PM (Gross 1991, Gross 1989, and Mikus 1989), the weighted mean of the calculated dose adjustment is a reduction to 58% of the normal dose (48%-66%; median 59%). This was rounded off to 50% to be more achievable in clinical practice. Flecainide has a narrow therapeutic range, which is why it is advisable to record an ECG and monitor the plasma concentration in the case of dose adjustment. Each method separately does not provide sufficient information.

IM: Based on three studies with a total of 23 IM (Hu 2012, Lim 2008, and Doki 2006), the weighted mean of the calculated dose adjustment is a reduction to 74% of the normal dose (58%-93%; median 81%). This was rounded off to 75% to be more achievable in clinical practice. Flecainide has a narrow therapeutic range, which is why it is advisable to record an ECG and monitor the plasma concentration in the case of dose adjustment. Each method separately does not provide sufficient information.

Recommendation concerning pre-emptive genotyping, including justification of choices:
The KNMP Pharmacogenetics Working Group considers genotyping before starting flecainide 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 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):
In a case report, a CYP2D6 PM with reduced renal function died due to flecainide toxicity (severity code F, corresponding to CTCAE grade 5) (Palmiere 2012). This results in the maximum score of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (2 points for CTCAE grade 5).
A severe clinical effect (severity code ≥ D, corresponding to CTCAE grade ≥ 3) was only found in two cases (Poh 2020 and Palmiere 2012). There were no 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 the second criterion of the clinical implication score: the level of evidence supporting an associated clinical effect grade ≥ 3 (only points for at least one study showing an association with a clinical effect grade ≥ 3).
A severe clinical effect only occurring in two cases also indicates that the number needed to genotype (NNG) to prevent one clinical effect code ≥ D (grade ≥ 3) is unlikely to be smaller than 1000. This results in a score of 0 of the maximum of 3 points for the third criterion of the clinical implication score: 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) Tambocor (flecainide) 26 June 2020 does not mention a CYP2D6 genotype or phenotype. This results in 0 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (only points for at least one genotype/phenotype mentioned in the SmPC).

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.

Source	Code	Effect	Comments
ref. 1 Poh BH et al. Complete heart block secondary to flecainide toxicity: is it time for CYP2D6 genotype testing? Pediatrics 2020;146:e20192608. PMID: 32561613.	2 IM: E	A preterm boy (born at 29 + 5/7 weeks' gestation) was treated with oral flecainide 2 mg/kg twice daily after developing supraventricular tachycardia for the second time at the age of 49 days. On day 7 of flecainide therapy, he developed heart block with widened QRS complex, resulting in bradycardia and a drop in oxygen saturation. Endotracheal and intravenous epinephrine, intravenous isoprenaline, sodium bicarbonate, and transcutaneous pacing failed to improve the heart rate. Extracorporeal membrane oxygenation was effective, as was treatment with intravenous lipid emulsion therapy for possible flecainide toxicity. After 16 hours of lipid emulsion therapy, arterial pulsatility returned, and both sinus rhythm and hemodynamic stability were achieved. Supraventricular tachycardia developing after the first 24 hours was successfully treated with sotalol. The boy was decannulated after 12 days. Because of prolonged cardiovascular collapse, he suffered from hypoxic-ischemic encephalopathy with extensive bilateral cystic encephalomalacia. The flecainide serum concentration taken approximately 24 hours after the last dose and while he was on extracorporeal membrane oxygenation was 1700 ng/ml (therapeutic range: 200-1000 ng/ml). Accidental overdose was ruled out after clarification with the nurses and by verifying the flecainide concentration in the suspension administered. The patients was genotyped for CYP2D6 two weeks after the last blood transfusion. His genotype was *10x2/*36 (gene dose 0.5). The patient did not use comedication that can prolong the QTc interval. Serum electrolytes around the time of cardiovascular collapse were within	Authors' conclusion: 'With this case report, we reinforce the importance of evaluating the CYP2D6 genotype before drug initiation in the neonatal population and recommend regular monitoring of serum flecainide levels and electrocardiograms in these patients.'

<table>
<tr><td>ref. 1, continuation</td><td></td><td>normal ranges, and cardiac enzymes were not elevated. In infants, the CYP2D6 enzyme becomes active in hours or days and may only reach complete maturation after 1 year of life. The administered dose was the right dose for a term neonates according to the Kinderformularium. However, the Kinderformularium does not indicate a dose for preterm neonates.</td><td></td></tr>
<tr><td>ref. 2
Calvo D et al.
Time-dependent responses to provocative testing with flecainide in the diagnosis of Brugada syndrome.
Heart Rhythm 2015;12:350-7.
PubMed PMID: 25460174.</td><td>3

Inactive or reduced active allele: AA#</td><td>The CYP2D6 genotype was determined for 11 responders to a flecainide provocation test, performed to investigate the presence of the Brugada syndrome.
Flecainide was administered as a single dose via continuous, intravenous infusion over 10 minutes. The dose was 2.0 mg/kg body weight to a maximum of 150 mg.
Brugada syndrome is characterised by a type I ECG pattern. Flecainide induces a type I ECG pattern in Brugada patients who do not exhibit this pattern spontaneously.
An early response was defined as a response in the first 10 minutes (during the flecainide infusion), a delayed response was defined as a response 10-30 minutes after the start of the infusion and a late response was defined as a response 90 minutes after the start of the infusion. As measurements are only performed for 30 minutes during a normal test, a late response can result in a missed diagnosis of Brugada syndrome, which is an important cause of sudden death in young adults. Those determining the response time were blinded for the end result of the provocation test and for data from which this result could be deduced.
Relevant co-medication was not excluded.

Genotyping:
- 5x gene dose 2
- 1x gene dose 1.5
- 4x gene dose 1.25
- 1x gene dose 1

Results:<table><tr><td colspan="3">Percentage of patients with gene dose < 2 for various response speeds:</td></tr><tr><td>early (n=4)</td><td>75%</td><td rowspan="3">S for the trend “late” versus “early” versus “delayed”</td></tr><tr><td>delayed (n = 3)</td><td>100%</td></tr><tr><td>late (n=4)</td><td>0%</td></tr></table></td><td></td></tr>
<tr><td>ref. 3
Palmiere C et al.
Usefulness of post-mortem biochemistry in forensic pathology: illustrative case reports.
Leg Med (Tokyo) 2012;14:27-35.
PubMed PMID: 22177826.</td><td>1

PM: F</td><td>A 69-year-old male weighing 69 kg, who had been using flecainide for several weeks, died suddenly. Three years previously, he had also used flecainide 100 mg/day for a short period due to paroxysmal supraventricular tachycardia. The plasma concentrations of flecainide were not determined at the time. Post-mortem examination revealed toxic concentrations of flecainide (6,100 µg/L in the blood, which is equivalent to 6.1 times the upper limit of the therapeutic range and 54,000 µg/L in the urine), whilst meta-O-desalkyl metabolites were virtually absent. The patient was found to be CYP2D6 PM. Post-mortem data also revealed that the patient had reduced renal function (intra-ocular fluid: elevated sodium concentrations (2% above the standard maxi-</td><td>Authors’ conclusion:
‘A case report is presented pertaining to fatal flecainide intoxication in a poor metabolizer also presenting an impaired renal function.’</td></tr>
</table>

<table>
<tr><td>ref. 3, continuation</td><td></td><td>mum value and 6% above the standard mean) and of urea, a less severely elevated concentration of creatinine and a low glucose concentration; urine: low sodium concentration (17% of that in the intra-ocular fluid)).
The authors concluded that the elevated plasma concentration of flecainide was caused by the combination of the PM genotype and the reduced renal function. Clearance via the kidneys is an important route for flecainide and there are indications that this is the most important elimination route in CYP2D6 PM.</td><td></td></tr>
<tr><td>ref. 4
Hu M et al.
Effects of CYP2D6 *10, CYP3A5*3, CYP1A2*1F, and ABCB1 C3435T polymorphisms on the pharmacokinetics of flecainide in healthy Chinese subjects.
Drug Metabol Drug Interact 2012;27:33-9.
PubMed PMID: 22718623.</td><td>3

IM: AA</td><td>15 healthy volunteers received a single dose of flecainide 100 mg. Co-medication, alcohol, grapefruit juice, herbal medicines and smoking were excluded.

Genotyping:
- 9x NM: - 4x gene dose 2
- 5x gene dose 1.25
- 6x IM: - 4x *10/*10
- 2x *5 heterozygote (1x *1/*5 and 1x *5/*10)

Results:
<table>
<tr><td colspan="3">AUC versus gene dose 2 (3383.3 ng.hour/mL):</td></tr>
<tr><td>gene dose 1.25</td><td>x 0.89</td><td rowspan="3">NS for the trend between the 4 groups and for gene dose 0.25-1.25 versus gene dose 2</td></tr>
<tr><td>*10/*10</td><td>x 1.09</td></tr>
<tr><td>*5 heterozygote</td><td>x 1.04</td></tr>
<tr><td>IM</td><td>x 1.07</td><td>NS</td></tr>
<tr><td colspan="3">The same result was observed after correction for the CYP3A5*3 polymorphism.</td></tr>
</table>
The authors indicated that the study did not have sufficient power to detect a significant difference between the CYP2D6 groups. In addition, the absence of the PM genotype, the large variation within - in particular - the group with gene dose 2 and a possible interaction with the CYP3A5*3 polymorphism contribute to the uncertainty. The percentage of patients with CYP3A5 *3/*3 was 100% for gene dose 2, 20% for gene dose 1.25 and 50% for *10/*10 and *5 heterozygote.

NOTE: Genotyping was performed for *2, *5 and *10. These are the most important alleles in this Chinese patient group.</td><td>Authors' conclusion:
'There was no significant difference in the pharmacokinetics of flecainide among CYP2D6 (mainly involving *10) genotypes.'

AUC flecainide versus gene dose 2:
IM: 107%</td></tr>
<tr><td>ref. 5
Lim KS et al.
Changes in the QTc interval after administration of flecainide acetate, with and without coadministered paroxetine, in relation to cytochrome P450 2D6 genotype: data from an open-label, two-period, single-sequence crossover study in healthy Korean male</td><td>3

IM: AA</td><td>For the 21 healthy volunteers in Lim 2008, the QT interval was measured at 11 time points on the day of taking flecainide and the day before. The QT interval was corrected using the formula by Fridericia (QT_{cF}), or individually using mixed-effects modelling (QT_{cI}).

Results:
<table>
<tr><td>Gene dose 0.25-0.5 versus gene dose 1.25 versus gene dose 2:</td></tr>
<tr><td>No difference in the elongation of:
- the corrected QT interval (either for QT_{cF}, or for QT_{cI}) (NS)
- the QRS duration (NS)
- the JT_c interval (=QTcF-QRS) (NS)</td></tr>
</table></td><td>Authors' conclusion:
'All genotype groups had significant increases from time-matched baseline in both the QTcF interval and the QTcI interval; the extent of increase did not differ significantly between groups.'</td></tr>
</table>

subjects. Clin Ther 2010;32:659-66. PubMed PMID: 20435235.		There were no severe side effects.	
ref. 6 Lim KS et al. Pharmacokinetic interaction of flecainide and paroxetine in relation to the CYP2D6*10 allele in healthy Korean subjects. Br J Clin Pharmacol 2008;66:660-6.	3 IM: A	21 healthy volunteers, 7x gene dose 2 (5x *1/*1, 2x *1/*2), 7x gene dose 1.25 (*1/*10), 7x gene dose 0.25-0.5 (6x *10/*10, 1x *10/*36), single dose of 200 mg flecainide, no co-medication, no smokers. Gene dose 0.25-0.5 versus gene dose 2: - increase in the AUC by 23% (NS, from 5715.5 to 7034.9 ng.h/mL). - increase in $t_{1/2}$ by 25% (S, from 10.0 to 12.5 h). Gene dose 1.25 versus gene dose 2: - increase in the AUC by 18% (NS, from 5715.5 to 6719.2 ng.h/mL). - increase in $t_{1/2}$ by 16% (NS, from 10.0 to 11.6 h). NOTE: genotyping was performed for *2, *4, *5, *10, *14, *21, *36, *41 and *2xN.	Authors' conclusion: 'In this study, we have shown that elimination half-life and MRT were significantly different among the three genotypic groups.' AUC flecainide versus gene dose 2: IM: 123%
ref. 7 Doki K et al. Effect of CYP2D6 genotype on flecainide pharmacokinetics in Japanese patients with supraventricular tachyarrhythmia. Eur J Clin Pharmacol 2006;62:919-26.	3 IM: A	58 patients with normal kidney and liver function, 17x NM (9x *1/*1, 6x *1/*2, 2x *2/*2), 28x NM + IM (20x *1/*10, 5x *2/*10, 1x *1/*5, 1x *1/*21, 1x *2/*5), 13x IM (10x *10/*10, 1x *10/*36, 1x *5/*36, 1x *21/*36), who used flecainide 1.4-5.0 mg/kg per day for a period of 1-91 months for supraventricular tachy-arrhythmia, no strong CYP2D6 inhibitors as co-medi-cation. 33 patients, 8x NM, 15x NM + IM, 10x IM, were men younger than 70 years. IM versus NM, men younger than 70: - increase in the dose-corrected trough concentra-tion by 72% (S, from 67 to 115 ng/mL per mg/kg). - decrease in the percentage of patients for whom the low clinical doses in Japan resulted in sub-therapeutic plasma concentrations (< 300 ng/mL) by 70% (NS, from 100% to 30%). (NM + IM) versus NM, men younger than 70: - increase in the dose-corrected trough concen-tration by 36% (NS, from 67 to 91 ng/mL per mg/kg). - decrease in the percentage of patients for whom the low clinical doses in Japan resulted in sub-therapeutic plasma concentrations (< 300 ng/mL) by 27% (NS, from 100% to 73%). NOTE: genotyping was performed for *2, *4, *5, *10, *14, *21, *36 and gene duplication.	Authors' conclusion: 'CYP2D6 genotype, even in IMs, as well as body weight, age, sex, and Scr influence flecainide pharmaco-kinetics in Japanese patients with supraventricular tachyarrhythmia.' dose-corrected trough concentration of flecainide versus gene dose 2: IM: 172%
ref. 8 Tenneze L et al. Pharmacokinetics and electrocardiographic effects of a new controlled-release form of flecainide acetate: comparison with the standard form and influence of	4	24 healthy study subjects, 4x PM and 20x NM[#] (phenotyped with dextromethorphan), no co-medication, various dosing regimens; - normal preparation 100 mg and 200 mg, single dose and multiple dosing 7 days - preparation with controlled release 100 mg and 200 mg, single dose and multiple dosing 7 days; *kinetic endpoints* - PM: the only parameter that differs significantly	Authors' conclusion: 'The CYP2D6 polymorphism did not appear to influence flecainide disposition kinetics or electrocardio-graphic effects at steady state.'

the CYP2D6 polymorphism. Clin Pharmacol Ther 2002;72:112-22. **ref. 8, continuation**	 PM: AA	versus NM# is t½ after a single dose of 100 mg normal preparation flecainide. *clinical endpoints* - PM: QRS elongation differs non-significantly versus NM# for none of the dosing regimens or preparations. NOTE: genotype unknown.	
ref. 9 Funck-Brentano C et al. Variable disposition kinetics and electrocardiographic effects of flecainide during repeated dosing in humans: contribution of genetic factors, dose-dependent clearance, and interaction with amiodarone. Clin Pharmacol Ther 1994;55:256-69.	4 PM: A	12 healthy study subjects, 5x PM and 7x NM# (phenotyped with dextromethorphan), 50-100 mg flecainide twice daily for 5 days, no co-medication; *kinetic endpoints* - PM: t½ is 15.7 hours at 50 mg twice daily and 17.6 hours at 100 mg twice daily, elevated for both doses versus NM#, by 26% and 44% respectively (both S). The C_{ss} of S-flecainide, R-flecainide and the sum differ non-significantly versus NM# for both doses. The log MR-dextromethorphan is correlated to the t½, but not to Cl_{or} or C_{ss} for flecainide. *clinical endpoints* (change in heart rate, QRS interval, PR interval, QT interval and JT interval): - PM: only PR interval differed significantly versus NM#, at 50 mg twice daily. NOTE: genotype unknown.	Authors' conclusion: 'Overall, these findings indicate that small differences in flecainide disposition kinetics persist at steady state between normal metabolizer and poor metabolizer subjects, however, because mean plasma concentration and effect of flecainide do not differ among subjects with both phenotypes, no specific dosing recommendation can be made on the basis of phenotype identificaton.'
ref. 10 Gross AS et al. Polymorphic flecainide disposition under conditions of uncontrolled urine flow and pH. Eur J Clin Pharmacol 1991;40:155-62.	3 PM: A	10 healthy study subjects, 5x PM and 5x NM# (phenotyped with sparteine), single dose of 50 mg flecainide, no co-medication; - PM: increase in the AUC for R-flecainide from 507 to 1195 h/mL·ng versus NM# (S by 136%), decrease in Cl_{or} from 783 to 313 mL/min (S by 60%), t½ is 19.2 hours. Increase in the AUC for S-flecainide from 548 to 1000 h/mL·ng (S by 83%), decrease in Cl_{or} from 828 to 379 mL/min (S by 54%), t½ is 15.8 hours. NOTE: genotype unknown	AUC R- + S-flecainide versus NM#: PM: 208%
ref. 11 Gross AS et al. Stereoselective disposition of flecainide in relation to the sparteine/debrisoquine metaboliser phenotype. Br J Clin Pharmacol 1989;28:555-66.	3 PM: A	10 healthy study subjects, 5x PM and 5x NM (phenotyped with sparteine, genotyped with *XbaI*), single dose of 50 mg flecainide, no co-medication; - PM: increase in the AUC for R-flecainide from 491 to 822 h/mL·ng versus NM (S by 67%), decrease in Cl_{or} from 768 to 467 mL/min (NS by 39%), t½ is 12.9 hours. Increase in the AUC for S-flecainide from 476 to 636 h/mL·ng (NS, by 34%), decrease in Cl_{or} from 793 to 620 ml/min (NS by 22%), t½ is 9.8 hours.	AUC R- + S-flecainide versus NM: PM: 151%
ref. 12 Mikus G et al. The influence of the sparteine/debrisoquin phenotype on the disposition of flecainide. Clin Pharmacol Ther 1989;45:562-7.	3 PM: A	10 healthy study subjects, 5x PM and 5x NM# (phenotyped with sparteine), single dose of 50 mg flecainide, no co-medication; - PM: increase in the AUC from 860 to 1462 h/mL·ng versus NM# (S by 70%), decrease in Cl_{or} from 1041 to 600 mL/min (S by 42%), t½ is 12 hours. NOTE: urine production and pH remained constant	AUC flecainide versus NM#: PM: 170%

ref. 12, continuation		NOTE: genotype unknown	

NM#: It is not possible to distinguish between NM, IM and UM based on phenotyping. NM# is therefore equal to NM + IM + UM.

Risk group	IMs with CYP2D6 inhibitors, IMs and PMs with reduced renal function

Comments:

- For the period after 2008, kinetic studies were only included if the clearance or (dose-corrected) exposure was determined per phenotype and the number of PM or IM is greater than 1 or the number of UM is greater than 0. For this reason, Doki K et al. Effects of CYP2D6 genotypes on age-related change of flecainide metabolism: involvement of CYP1A2-mediated metabolism. Br J Clin Pharmacol 2009;68:89-96. PubMed PMID: 19660006 and Doki K et al. CYP2D6 genotype affects age-related decline in flecainide clearance: a population pharmacokinetic analysis. Pharmacogenet Genomics 2012;22:777-83. PubMed PMID: 22941032 were not included. The first study found reduced metabolite formation in patients from 70 years upwards compared to patients younger than 70 years for a group of 19 IM and 2 PM and for a group of 51x gene dose 1.5 and 5x gene dose 1, but not for a group with gene dose 2. However, the dose-corrected plasma concentration of flecainide did not differ significantly between the age groups for IM+PM. When creating a pharmacokinetic model, the second study found a reduced clearance for IM+PM at an age from 55 years upwards and for gene dose 1 + gene dose 1.5 at an age from 60 years upwards. The authors attributed this to a greater contribution of the metabolism of CYP1A2 at gene doses lower than 2. CYP1A2 metabolises flecainide *in vitro* and the activity of CYP1A2 decreases with age.

Date of literature search: 16 May 2022.

	Phenotype	**Code**	**Gene-drug interaction**	**Action**	**Date**
KNMP Pharmacogenetics Working Group decision	PM	4 F	yes	yes	12 September 2022
	IM	3 E	yes	yes	
	UM	--	yes	yes	

Mechanism:

The R-enantiomer of flecainide is metabolised by CYP2D6, the S-enantiomer is metabolised via other routes. This results in the formation of the pharmacologically inactive metabolites meta-O-desalkyl flecainide and meta-O-desalkyl lactam flecainide.
According to the NVZA, the therapeutic range of flecainide is 200-1000 ng/ml (trough concentrations) or 750-1250 ng/ml (peak concentrations), while trough concentrations > 1000 ng/ml are toxic.

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