CYP2C19: imipramine 1913 to 1915

AUC = area under the plasma concentration-time curve, Cl_{or} = oral clearance, C_{ss} = steady-state concentration, DES = desipramine, EM = extensive metaboliser (*1/*1, *1/*17) (normal CYP2C19 enzyme activity), IM = intermediate metaboliser (*1/*2, *1/*3, *2/*17, *3/*17) (reduced CYP2C19 enzyme activity), IMI = imipramine, MR = metabolic ratio, NS = non-significant, PM = poor metaboliser (*2/*2, *2/*3, *3/*3) (absent CYP2C19 enzyme activity), r_s = correlation coefficient, S = significant, SmPC = summary of product characteristics, TCA = tricyclic antidepressant, UM = ultra-rapid metaboliser (*17/*17) (increased CYP2C19 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:
The primary metabolic routes for imipramine are N-methylation mainly by CYP2C19 to the active metabolite desipramine and hydroxylation by CYP2D6 to 2-hydroxy-imipramine. Desipramine is metabolised by CYP2D6 to 2-hydroxy-desipramine. The therapeutic effectiveness and side effects of imipramine are associated with the plasma concentration of the sum of imipramine and desipramine. The therapeutic range is 150-300 ng/ml and summed plasma concentrations above 500 ng/ml are considered to be toxic.
The primary effects found for all phenotypes were effects on imipramine AUC and C_{ss}. The effects on imipramine+desipramine AUC and C_{ss}, which determine the therapeutic effectiveness and side effects, were smaller and there was little evidence of significance. Patients with absent CYP2C19 enzyme activity (poor metabolisers (PM)) showed the largest effect and PM was also the only phenotype for which a study showed a significant effect on imipramine+desipramine exposure (Koyama 1996). Because the therapeutic effectiveness and side effects of imipramine have been shown to be associated with the plasma concentration of the sum of imipramine and desipramine and because of the relatively narrow therapeutic range, the KNMP Pharmacogenetics Working Group decided to recommend dose adjustment in PM (yes/yes-interaction). However, for patients with reduced or enhanced CYP2C19 activity (intermediate or ultra-rapid metabolisers (IM or UM)), the effect was too limited to consider dose or therapy adjustment meaningful (yes/no-interactions).
A detailed justification of choices is given below.

PM: A small study that investigated the effect of CYP2C19 polymorphisms on therapeutic effect and side effects of imipramine did not find significant effects (Morinobu 1997; 5 PM). The PM phenotype was found to increase imipramine+desipramine AUC and C_{ss}, but these increases were only significant in one of the four studies (Koyama 1996, Koyama 1994, Morinobu 1997 and Schenk 2010). As the therapeutic effectiveness and side effects of imipramine are associated with the plasma concentration of the sum of imipramine and desipramine, dose adjustment or use of an alternative is desirable if the effect is sufficiently large. The weighted mean of the dose adjustment calculated on the basis of the increase in imipramine+desipramine AUC and C_{ss} for a total of 20 PM is a dose reduction to 71% of the standard dose (range 54-85%; median 72%). This was translated to 70% to be more achievable in clinical practice.

IM: A quantitative effect on imipramine+desipramine exposure for IM patients was only found in one study, and this effect was not significant (Schenk 2010; 45 IM). On theoretical grounds, this effect will be smaller than for PM patients and the dose adjustment calculated on the basis of the study is a reduction by 22% to 78% of the standard dose. This decrease in dose adjustment is small compared to the width of the therapeutic range (the therapeutic imipramine+desipramine C_{ss} is between 150-300 ng/mL; this means that there is a 100% margin between the lower and upper limits of the therapeutic range), which is why dose adjustment is not considered meaningful.

UM: There is only one study for UM patients (Schenk 2010; 11 UM). This study identified a non-significant quantitative effect on imipramine+desipramine exposure. There was only a significant effect of *17 on imipramine+desipramine C_{ss} in multivariate analysis. The dose adjustment calculated on the basis of the study is an increase by 16% to 116% of the standard dose. Given this limited effect and the limited evidence for significance of the change in imipramine + desipramine C_{ss}, dose adjustment is not considered meaningful.

You can find a detailed overview of the observed kinetic and clinical effects per phenotype in the background information text of the gene-drug interactions on the KNMP Kennisbank. You might also have access to this background 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 imipramine to be potentially beneficial. 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 0 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 observed in users of imipramine 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 association with clinical effects with a severity code ≥ D corresponding to CTCAE grade ≥ 3).
The lack of 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 imipramine does not mention a CYP2C19 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 uses the KNMP nomenclature for EM, PM, IM and UM. As a result, the definitions of EM, PM, IM and UM in the table below can differ from the definitions used by the authors in the article.

Source	Code	Effect	Comments
ref. 1 Schenk PW et al. The CYP2C19*17 genotype is associated with lower imipramine plasma concentrations in a large group of depressed patients. Pharmacogenomics J 2010;10:219-25.	4 PM: A IM: A UM: A	The data from 178 patients from the Schenk et al., 2008 study (117x EM (65x *1/*1, 52x *1/*17), 45x IM (32x *1/*2, 13x *2/*17), 5x PM (*2/*2), 11x UM (*17/*17)) were reanalysed after genotyping for *17. *2/*2 versus *1/*2 versus *2/*17 versus *1/*1 versus *1/*17 versus *17/*17: - Imipramine[b] C_{ss} decreased with gene activity (0.91 versus 0.78 versus 0.69 versus 0.60 versus 0.52 versus 0.43 ng/mL per mg) (S) - No difference in (imipramine + desipramine)[b] C_{ss} (1.43 versus 1.60 versus 1.48 versus 1.31 versus 1.11 versus 1.05 ng/mL per mg) (NS) - Multivariate analysis found a limited effect of *17 on (imipramine + desipramine) C_{ss} (S), but univariate analysis did not show an effect (NS) *1/*1 versus *1/*17 versus *17/*17 (after exclusion of CYP2D6 PM and UM): - Imipramine[b] C_{ss} decreased with the number of *17 alleles (0.64 versus 0.52 versus 0.45 ng/mL per mg) (S) - No difference in (imipramine + desipramine)[b] C_{ss} (1.32 versus 1.14 versus 1.00 ng/mL per mg) (NS) PM versus IM versus EM versus UM: - No difference in (imipramine + desipramine)[b] C_{ss} (1.43 versus 1.57 versus 1.22 versus 1.05 ng/mL per mg) (NS)	Authors' conclusion: "In a multivariate analysis, we found a significant, but limited effect of the CYP2C19*17 genotype on imipramine + desipramine concentrations. …….. CYP2C19*17 genotyping will, in our view, not importantly contribute to dose management of patients on imipramine therapy guided by imipramine+desipramine plasma concentrations." Imipramine+desipramine plasma concentration versus EM: IM: 128% PM: 117% UM: 86%
ref. 2 Schenk PW et al. Association of graded allele-specific changes in CYP2D6 function with imipramine dose requirement in a large group of	4 PM: A	181 patients (130x *1/*1, 46x *1/*2, 5x *2/*2) received imipramine 40-900 mg/day; relevant co-medication was excluded. The imipramine dose was based on a target of 200-300 ng/mL for IMI+DES C_{ss}. PM versus IM versus EM: - Imipramine[b] C_{ss} decreased with the number of active alleles (0.91 versus 0.75 versus 0.55	Authors' conclusion: "The contribution of the CYP2C19*2 polymorphism to the prediction of either the IMI+DESI plasma level, IMI dose administered at steady state or drug dose

depressed patients. Mol Psychiatry 2008;13:597-605. **ref. 2, continuation**	IM: A	ng/mL per mg) (S) - No difference in (imipramine + desipramine)[b] C_{ss} (1.43 versus 1.56 versus 1.21 ng/mL per mg) (NS) Note: genotyping was only performed for *2 (responsible for 70% of PM in Caucasians)	requirement was not statistically significant."
ref. 3 Morinobu S et al. Effects of genetic defects in the CYP2C19 gene on the N-demethylation of imipramine, and clinical outcome of imipramine therapy. Psychiatry Clin Neurosci 1997;51:253-7.	3 PM: A	10 patients (5x EM; 5x PM (2x *2/*2, 3x *2/*3)) received imipramine 0.745-2.174 mg/kg twice daily for 4 weeks. There were no significant differences in imipramine dose between the EM and PM groups. Co-medication with flunitrazepam was permitted if necessary. PM versus EM: - Imipramine[a] C_{ss} increased from 0.0084 to 0.0194 ng/mL per mg/kg (S by 131%) - Desipramine[a] C_{ss} decreased from 0.0091 to 0.0052 ng/mL per mg/kg (NS by 43%) - Hydroxyimipramine[a] C_{ss} increased from 0.0024 to 0.0076 ng/mL per mg/kg (S by 217%) - Desipramine/imipramine MR decreased from 1.220 to 0.270 ng/mL per mg/kg (S by 78%) - Hydroxydesipramine/hydroxyimipramine MR decreased from 2.098 to 0.279 ng/mL per mg/kg (S by 87%) - Therapeutic effect increased from 51.0% to 56.1% (NS by 10%) - Decreased score on the UKU Side Effect Rating Scale from 2.40 to 1.40 (NS by 42%)	Authors' conclusion: "The results of this study suggest that determination of mutations in the CYP2C19 gene may not be of clinical importance in predicting the therapeutic response to or the side effects of imipramine. However, previous studies demonstrated that levels of imipramine positively correlated with the therapeutic response and severity of side effects." Imipramine+desipramine plasma concentration versus EM: PM: 141%
ref. 4 Madsen H et al. Imipramine demethylation in vivo: impact of CYP1A2, CYP2C19, and CYP3A4. Clin Pharmacol Ther 1997;61:319-24.	3 IM: A PM: A	32 healthy volunteers received a single dose of 25 mg imipramine, urine was collected for 24 hours and metabolite levels measured. All volunteers were CYP2C19 EM* and CYP2D6 PM (n=31) or very poor EM* (n=1). Co-medication was variable. - There was a negative correlation between S/R mephenytoin MR and the two N-demethylation ratios (desipramine/imipramine and 2-hydroxydesipramine/2-hydroxyimipramine) (S). - CYP2C19 activity as measured by the S/R mephenytoin MR was responsible for 19% of N-demethylation of imipramine to desipramine and 29% of N-demethylation of 2-hydroxyimipramine to 2-hydroxydesipramine in vivo. Note: genotype unknown	Authors' conclusion: "CYP2C19 seemed to be responsible for the N-demethylation of imipramine (19%) and 2-hydroxyimipramine (30%) but from this in vivo study we found no sign of CYP1A2 or CYP3A4 to be involved in the N-demethylation of imipramine or 2-hydroxyimipramine."
ref. 5 Koyama E et al. Steady-state plasma concentrations of imipramine and desipramine in relation to S-mephenytoin 4'-hydroxylation status in Japanese depressive patients. J Clin Psychopharmacol 1996;16:286-93.	3 PM: A	28 patients (23x EM* and 5x PM; all CYP2D6 EM*) received imipramine 25-75 mg/day (0.39-1.39 mg/kg per day) for 2 weeks. Temporary co-medication with benzodiazepines had no effect on imipramine pharmacokinetics in EMs. PM versus EM+IM: - Imipramine[a] C_{ss} increased from 0.0041 to 0.0193 ng/mL per mg/kg (S by 371%) - Imipramine+desipramine[a] C_{ss} increased from 0.0132 to 0.0244 ng/mL per mg/kg (S by 85%) - Mean demethylation index (desipramine/imipramine MR) decreased from 0.705 to 0.271 (S by 62%) - Desipramine[a] C_{ss} did not decrease (0.0052 versus 0.0051 ng/mL per mg/kg) (NS by 2%) Negative correlations with CYP2C19 activity as	Authors' conclusion: "By taking into account that the incidence of the PMs of CYP2C19 is much greater (18-23%) than that of CYP2D6 (<1%) in Japanese population, the individually predetermined assessment of the CYP2C19-mediated metabolic capacity of imipramine would be more valuable than that of the CYP2D6-mediated capacity for forecasting

ref. 5, continuation	IM: A	measured by S-mephenytoin metabolism: - Imipramine[a] C_{ss} (S) - Imipramine+desipramine[a] C_{ss} (S) Positive correlation with CYP2C19 activity as measured by S-mephenytoin metabolism: - Desipramine/imipramine MR (S) Note: genotype unknown	the steady-state concentrations of imipramine and desipramine in Japanese depressive patients." Imipramine+desipramine plasma concentration versus EM+IM: PM: 185%
ref. 6 Madsen H et al. Imipramine metabolism in relation to the sparteine and mephenytoin oxidation polymorphisms--a population study. Br J Clin Pharmacol 1995;39:433-9.	3 IM: A PM: A	327 healthy volunteers (324x EM*, 3x PM) received a single dose of 25 mg imipramine, urine was collected for 24 hours and metabolite levels measured. No co-medication. - There was a weak negative correlation between S/R mephenytoin MR and the two N-demethylation ratios (desipramine/imipramine and 2-hydroxydesipramine/2-hydroxyimipramine) (S). - The demethylation ratios were higher in smokers than in non-smokers, which suggests a role of CYP1A2 in imipramine N-demethylation. Note: genotype unknown	
ref. 7 Koyama E et al. Metabolic disposition of imipramine in oriental subjects: relation to metoprolol alpha-hydroxylation and S-mephenytoin 4'-hydroxylation phenotypes. J Pharmacol Exp Ther 1994;271:860-7.	3 PM: A IM: A	16 healthy volunteers received a single dose of 25 mg imipramine, and metabolite levels were measured in plasma and urine. Of the 12 volunteers with the CYP2D6 EM* phenotype, there were 7 EM* and 5 PM for CYP2C19. No co-medication. Smoking unknown. PM versus EM+IM: - Imipramine AUC_{∞} increased from 215 to 375 ng.h/mL (S by 74%) - Desipramine AUC decreased from 111.8 to 68.2 ng.h/mL (S by 39%) - (Imipramine + desipramine) AUC increased from 326.8 to 443.2 ng.h/mL (significance not known; by 36%) - Desipramine/imipramine AUC ratio decreased from 0.52 to 0.18 (S by 65%) - Imipramine Cl_{or} decreased from 30.1 to 15.6 mL/min per kg (S by 48%) Positive correlations with CYP2C19 activity as measured by 4'-hydroxymephenytoin secretion: - Desipramine AUC (S) - Desipramine/imipramine AUC ratio (S) There was no significant correlation with (imipramine + desipramine) AUC. The data derived from the metabolites present in urine were nicely consistent with data obtained from plasma. Note: genotype unknown	Authors' conclusion: "The results suggest that the 2-hydroxylation and the N-demethylation of imipramine metabolism are under a pharmacogenetic control of debrisoquin- and S-mephenytoin-type oxidation, respectively, in Oriental subjects." Imipramine+desipramine AUC versus EM+IM: PM: 136%
ref. 8 Skjelbo E et al. The N-demethylation of imipramine correlates with the oxidation of S-mephenytoin (S/R-ratio). A population study. Br J Clin Pharmacol	3 PM: A IM: A	106 volunteers (104x EM*, 2x PM; all CYP2D6 EM) received a single dose of 25 mg imipramine. - There was a negative correlation between S/R mephenytoin MR and the two N-demethylation ratios (desipramine/imipramine and 2-hydroxydesipramine/2-hydroxyimipramine) (S). Note: genotype unknown	Authors' conclusion: "These findings confirm those of an earlier panel study showing that the demethylation of imipramine and 2-OH-imipramine cosegregates in part with the mephenytoin oxidation

1993;35:331-4.			polymorphism."
ref. 9 Skjelbo E et al. The mephenytoin oxidation polymorphism is partially responsible for the N-demethylation of imipramine. Clin Pharmacol Ther 1991;49:18-23.	3 PM: A	22 volunteers (16x EM*, 6x PM; all CYP2D6 EM) received a single dose of 100 mg imipramine (n=21) or a single dose of 50 mg imipramine (n=1; PM for both CYP2D6 and CYP2C19). All volunteers had mild side effects (sedation, dry mouth, dizziness). The double PM had the lowest Cl_{or}: 0.66 L/min. PM versus EM+IM: - Clearance by demethylation decreased from 1.43 to 0.74 L/min (S by 48%) - Total clearance (Cl_{or}) decreased from 2.48 to 1.83 L/min (NS by 26%) - Desipramine/imipramine MR decreased from 1.26 to 0.39 (S by 69%) Note: genotype unknown	Authors' conclusion: "This and an earlier study show that the oxidation of imipramine is mediated by means of two different polymorphic P450 isozymes, 2-hydroxylation by way of the sparteine oxygenase (P450IID6) and demethylation by way of the mephenytoin oxygenase (P450IIC8)."

[#] Phenotyping did not distinguish between IM and EM. EM* is therefore EM+IM.
[a] Corrected for dose and body weight.
[b] Corrected for dose.

Risk group	CYP2D6 PM, CYP2D6 inhibitors, CYP2C19 inhibitors

Comments:=

- The therapeutic effectiveness and side effects of imipramine are associated with the plasma concentration of the sum of imipramine and desipramine (Glassman AH et al. Clinical implications of imipramine plasma levels for depressive illness. Arch Gen Psychiatry 1977;34:197-204 and Reisby N et al. Imipramine: clinical effects and pharmacokinetic variability. Psychopharmacology 1977;54:363-72 and Rudorfer MV et al. Pharmacokinetics of antidepressants. In: Psychopharmacology: The Third Generation Progress, ed. by HY Meltzer, pp. 1353-63. Raven Press, New York, 1987. and Sallee FR et al. Clinical pharmacokinetics of imipramine and desipramine. Clin. Pharmacokinet 1990;18:346-64.).
- The status report includes both genotyping and phenotyping studies. In order to distinguish between these two types of studies, any phenotyping studies include 'Note: genotype unknown' as the last line.
- Possible relationship between CYP2C19 polymorphisms and depression:
  - Jukić MM et al. Elevated CYP2C19 expression is associated with depressive symptoms and hippocampal homeostasis impairment. Mol Psychiatry 2017;22:1155-1163. PubMed PMID: 27895323.
    This publication is from the same group as Sim 2010.
    In a cohort of 3849 urban African-Americans of low economic status, the 123 CYP2C19*2/*2 subjects had a decrease in major depressive disorder prevalence compared to the other subjects with at least one active CYP-2C19 allele (23% versus 32%) (S). In addition, there was a trend for a lower Beck's Depression Inventory (BDI) score in the CYP2C19*2/*2 subjects compared to the other subjects (p = 0.074). However, the lifetime stress exposure was much larger in the African-American cohort compared with the previously analysed Swedish cohort (Sim 2010), thereby increasing the BDI score variability. After the most traumatized subjects (perceived stress scale score at higher quartile and above) were exempted from the analysis to better match the two samples, the BDI score reduction was significant (effect size = - 2.05 (-24.61%)) (S).
    In order to test whether the CYP2C19 genotype influences suicidality in patients with major depressive disorder, CYP2C19 genotype was tested as a predictor for suicide intent in 209 Western European suicide attempters with major depressive disorder. As there were only two CYP2C19*2/*2 allele carriers in the cohort, it was not possible to test whether this genotype affects Beck's suicide intent scale-objective circumstances (SIS-OS) score. However, in a complementary exploratory analysis, the SIS-OS score seemed to vary between different CYP2C19 genotypes with a decrease for *2/*2 versus *1/*1 versus *1/*2 versus *2/*17 versus *17/*17 versus *1/*17. Further analysis showed that SIS-OS score was not significantly affected by the presence of the CYP2C19*2 allele, whereas it was significantly increased in CYP2C19*17 allele carriers (119 versus 90 subjects, effect size = +1.36 (+25.69%)) (S). Since the score was lower for the 8 patients with genotype *17/*17 compared to the patients with genotype *1/*17, this significant effect seemed to be mainly driven by the *1/*17 genotype. The classification of the suicide attempters to severe (SIS-OS score at higher quartile and above) and non-severe, yielded a higher frequency of patients with *17 allele among severe suicide attempters (S).
    The authors conclude that the CYP2C19*2/*2 genotype associates with a phenotype more resilient to major depressive disorder and that the CYP2C19*17 allele may be a risk allele for suicidality in major depressive disorder. They indicate that a major limitation of the suicidality study is the absence of information regarding the indi-

viduals' drug treatment and their drug plasma levels. Therefore, it was not possible to determine whether the observed relationship was caused by endogenous or drug-metabolic CYP2C19-mediated effects.

- Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium. A mega-analysis of genome-wide association studies for major depressive disorder. Mol Psychiatry 2013;18:497-511. PubMed PMID: 22472876.
  A mega-analysis of genome-wide association studies found no significant association between the risk of depression and CYP2C19.
- Sim SC et al. Association between CYP2C19 polymorphism and depressive symptoms. Am J Med Genet B Neuropsychiatr Genet. 2010;153B:1160-6.
  In a group of 1472 Europeans older than 44 years (1017x EM (637x *1/*1, 380x *1/*17), 375x IM (290x *1/*2, 85x *2/*17), 35x PM (*2/*2), 45x UM), significantly lower depressive symptoms (measured on the Center of Epidemiologic Studies Depression (CES-D) scale) were found among PM patients than among *1/*1. There was only a difference among people younger than 73 years and among men. The effect size was in the same order of magnitude as that observed between non-users and users of antidepressants. The authors stated that CYP2C19 polymorphisms may have an effect on depressive symptoms in adult Europeans.

- Existing guideline:

Hicks JK et al. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther 2016 Dec 20 [Epub ahead of print]. PubMed PMID: 27997040.

CPIC uses the same definitions of IM, PM and UM as we do. CPIC assigns *2/*17 and *3/*17 to the IM phenotype, because the currently available evidence indicates that the CYP2C19*17 increased function allele is unable to completely compensate for the CYP2C19 no function alleles, but indicates that this is a provisional classification, However, CPIC uses a different definition for EM (only *1/*1) and changed the name of this phenotype to normal metaboliser (NM). CPIC created a new phenotype rapid metaboliser (RM) for *1/*17. CPIC also has nomenclature, but no recommendations for genotypes with very uncommon alleles with lower activity, e.g. *9 and *10. The summary below uses the KNMP definitions for EM, PM, IM and UM.

CPIC uses amitriptyline as a representative TCA for this guideline. CPIC states that the results of the amitriptyline studies may apply to other TCAs because these drugs have comparable pharmacokinetic properties (the reviews Rudorfer MV et al. Metabolism of tricyclic antidepressants. Cell Mol Neurobiol 1999;19:373-409 and Stingl JC et al. Genetic variability of drug-metabolizing enzymes: the dual impact on psychiatric therapy and regulation of brain function. Mol Psychiatry 2013;18:273-87). In addition, extrapolated dose adjustments based on metaboliser status are similar across the tricyclic class (Stingl 2013).

For amitriptyline, CPIC states that the usual starting dose may be used in CYP2C19 *1/*1 and IM. Although CYP2C19 IM would be expected to have a modest increase in the ratio of amitriptyline to nortriptyline plasma concentrations, the evidence does not indicate that CYP2C19 IM should receive an alternate dose. CPIC states that patients taking amitriptyline who are CYP2C19 *1/*17 or UM may be at risk for having low plasma concentrations and an imbalance between parent drug and metabolites causing treatment failure and/or adverse events. However, CPIC states that the CYP2C19*17 allele did not alter the sum of amitriptyline plus nortriptyline plasma concentrations. Despite this, CPIC states that extrapolated pharmacokinetic data suggest that CYP2C19 *1/*17 or UM may need a dose increase. In addition, CPIC indicates that the CYP2C19*17 allele was associated with higher nortriptyline plasma concentrations, possibly increasing the risk of adverse events. However, nortriptyline is registered for use in depression and neuropathic pain itself. Therefore, it seems unlikely that an increased conversion of amitriptyline into nortriptyline would result in an increase in adverse events necessitating therapy adjustment. CPIC states that due to the need for further studies investigating the clinical importance of CYP2C19*17 regarding TCA metabolism and the possibility of altered concentrations, they recommend considering an alternative TCA or other drug not affected by CYP2C19. Due to limited available data, this recommendation is classified as optional (i.e. the desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action). CPIC states that if amitriptyline is administered to a CYP2C19 *1/*17 or UM, therapeutic drug monitoring is recommended. CPIC states that CYP2C19 PM are expected to have a greater ratio of amitriptyline to nortriptyline plasma concentrations. The elevated amitriptyline plasma concentrations may increase the chance of a patient experiencing side effects. CPIC recommends to consider a 50% reduction of the usual amitriptyline starting dose along with therapeutic drug monitoring.

Because the TCAs have comparable pharmacokinetic properties, CPIC states that it may be reasonable to extrapolate the amitriptyline guideline to other TCAs, including imipramine, with the acknowledgment that there are fewer data supporting dose adjustments for these drugs than for amitriptyline.

Thus, the therapeutic recommendations for imipramine are identical to the therapeutic recommendations for amitriptyline with only the classification of the recommendations adapted to the fewer supporting clinical and pharmacokinetic data:

Dosing recommendations for imipramine for conditions requiring higher doses such as depression based on CYP2C19 phenotype[a,b]		
Phenotype	Therapeutic recommendation	Classification of recommendation
UM	Avoid imipramine use due to potential for sub-optimal response. Consider alternative drug not metabolised by CYP2C19. TCAs without	Optional[d,e]

	major CYP2C19 metabolism include the secondary amines nortriptyline and desipramine. If imipramine is warranted, utilise therapeutic drug monitoring to guide dose adjustments.[f]	
*1/*17	Avoid imipramine use due to potential for sub-optimal response. Consider alternative drug not metabolised by CYP2C19. TCAs without major CYP2C19 metabolism include the secondary amines nortriptyline and desipramine. If imipramine is warranted, utilise therapeutic drug monitoring to guide dose adjustments.[f]	Optional[d,e]
*1/*1	Initiate therapy with recommended starting dose.[c]	Strong
IM	Initiate therapy with recommended starting dose.[c]	Optional[d]
PM	Avoid imipramine use due to potential for sub-optimal response. Consider alternative drug not metabolised by CYP2C19. TCAs without major CYP2C19 metabolism include the secondary amines nortriptyline and desipramine. For imipramine, consider a 50% reduction of the recommended starting dose.[c] Utilise therapeutic drug monitoring to guide dose adjustments.[f]	Optional[d]

[a] Dosing recommendations only apply to higher initial doses of TCAs for treatment of conditions such as depression. For conditions at which lower initial doses are used, such as neuropathic pain, CPIC does recommend no dose modifications for PM or IM, because it is less likely that PM or IM will experience adverse effects due to supratherapeutic plasma concentrations of the TCA. However, CPIC indicates that these patients should be monitored closely for side effects. In addition, if larger doses of TCA are warranted, CPIC recommends following the gene-based dosing guidelines in the table above. For *1/*17 and UM, CPIC recommends considering an alternative agent, because pharmacokinetic data predict these patients to be at risk of failing TCA therapy for neuropathic pain.

[b] Because the tricyclics have comparable pharmacokinetic properties, it may be reasonable to apply these amitriptyline recommendations to other tricyclics, including imipramine, with the acknowledgment that there are fewer data supporting dose adjustments for these drugs than for amitriptyline.

[c] Patients may receive an initial low dose of a TCA, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose.

[d] The classification optional indicates that the desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.

[e] Although the total concentration of amitriptyline and nortriptyline may be unchanged for a CYP2C19 ultra-rapid or poor metaboliser in certain instances, an imbalance between serotonergic and noradrenergic affect could influence clinical response or toxicities. There is limited evidence demonstrating that a serotonergic/noradrenergic imbalance influences outcomes, thus contributing to the classification of recommendations as optional.

[f] Titrate dose to observed clinical response with symptom improvement and minimal (if any) side effects.

As evidence linking CYP2C19 genotype with imipramine phenotype, CPIC mentions Schenk 2010, Schenk 2008, Madsen 1997, Morinobu 1997, Koyama 1996, Madsen 1995, Koyama 1994, Skjelbo 1993 and Skjelbo 1991. All these studies are included in our risk analysis. CPIC indicates that these studies provide a high level of evidence for a decreased imipramine metabolism in PM compared to *1/*1 and for a correlation of the metabolism of the CYP-2C19 probe drug mephenytoin with imipramine metabolism. The studies provide a moderate level of evidence for a decreased imipramine metabolism in IM compared to *1/*1 and for an increased imipramine metabolism in UM compared to *1/*1.

CPIC also took other gene-based dosing recommendations in consideration, including the 2008 and 2011 publications of our dosing recommendations in Clinical Pharmacology and Therapeutics.

CPIC also provides therapeutic recommendations based on both CYP2D6 and CYP2C19 genotypes. For CYP2D6 UM and for CYP2D6 PM the therapeutic recommendations for the different CYP2C19 phenotypes are similar, reflecting the stronger influence of the CYP2D6 phenotype compared to the CYP2C19 phenotype. CPIC indicates that further studies are needed to develop moderate or strong dosing recommendations for TCAs when considering combined CYP2D6/CYP2C19 phenotypes. At the moment, insufficient data are available.

On 25-4-2018, there was not a more recent version of the recommendations present on the PharmGKB- and on the CPIC-site.

Date of literature search: 20 april 2018.

	Phenotype	Code	Gene-drug interaction	Action	Date
Dutch Pharmacogenetics Working Group decision	IM	4 A	Yes	No	10 September 2018
	PM	4 A	Yes	Yes	
	UM	4 A	Yes	No	

Mechanism:

The primary metabolic routes for imipramine are N-methylation mainly by CYP2C19 to the active metabolite desipra-

mine and hydroxylation by CYP2D6 to 2-hydroxy-imipramine. Desipramine is metabolised by CYP2D6 to 2-hydroxy-desipramine.
The therapeutic effectiveness and side effects of imipramine are associated with the plasma concentration of the sum of imipramine and desipramine. The therapeutic range is 150-300 ng/ml and values above 500 ng/ml are considered to be 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 genotype 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+	0+
Corresponding Clinical Implication Score:		Potentially beneficial