CYP2C19: citalopram 4195 to 4197

AUC = area under the concentration-time curve, CI = confidence interval, Cl_{or} = oral clearance, C_{ss} = plasma concentration in steady state, CT = citalopram, EM = extensive metaboliser (*1/*1, also called homozygous EM or homEM in references, *1/*17) (normal CYP2C19 enzyme activity), IM = intermediate metaboliser (*1/*2, *1/*3, also called heterozygous EM or hetEM in references, *17/*2, *17/*3) (reduced CYP2C19 enzyme activity), MR = metabolic ratio, NS = non-significant, PM = poor metaboliser (*2/*2, *2/*3, *3/*3) (absent CYP2C19 enzyme activity), QT_c interval = heart rate corrected QT-interval, S = significant, SmPC = summary of product characteristics, 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:
CYP2C19 converts citalopram to a metabolite with limited anti-depressant activity. The citalopram dose required for therapeutic or supra-therapeutic plasma concentrations is therefore lower for patients with reduced CYP2C19 activity (IM and PM) and higher for patients with increased CYP2C19 activity (UM). Studies have shown a distinct effect on citalopram plasma concentrations in IM, PM and UM patients. However, citalopram has a broad therapeutic range.

UM: There were no significant effects on remission, tolerance, dose that was set for the patient and dose-corrected plasma concentration. No warning is therefore required for this gene-drug interaction (yes/no-interaction).

IM and PM: The altered kinetics in IM and PM for CYP2C19 do not appear to result in an increase in side effects. One study found an increase in the risk of intolerance for IM + PM. However, this study also found an increased chance of remission for tolerant PM. Another study found a larger QT_c interval for IM+PM (and a trend for a larger QT_c interval for IM). This study found no effect of plasma concentration and dose on QT_c interval, but another study did find an increase with the dose (Castro VM et al. QT interval and antidepressant use: a cross sectional study of electronic health records. BMJ 2013;346:f288). Therefore, it was decided to issue a warning (yes/yes-interactions). The recommendation is to lower the maximum dose in IM and PM patients to such an extent, that the citalopram plasma concentrations at maximum dose and thus the risk of QT-prolongation and risk of ineffectiveness are the same in EM, IM and PM.

You can find a detailed overview of the observed kinetic and clinical effects in the background information text of the gene-drug interactions on the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.
Substantiation for the dose recommendation for IM and PM patients is provided below.
Justification of dose recommendation
Dose adjustments have been calculated based on citalopram AUC or C_{ss}.
Where the effect is only known versus EM + UM (e.g. in Fudio 2010), the effect of EM + UM is assumed to be similar to that of EM, due to the much lower prevalence of UM.

PM: The weighted mean of the calculated dose adjustment for PM is a dose reduction to 74% (46-108%; median 70%). This is 48%, based on the AUC increase reported by the FDA. As the distribution in the results from these studies is very high and the FDA data in all likelihood are based on more patients, the decision was made to use the FDA data. The reduction of the maximum dose for PM was translated to 50% to be more achievable in clinical practice. This is equivalent to a maximum dose of 20 mg/day up to age 65 years and 10 mg/day for 65 years and older. This is equivalent to 16 mg/day and 8 mg/day for the drops, which have a higher bioavailability.

IM: The weighted mean of the calculated dose adjustment for IM is a dose reduction to 71% (61-95%; median 72%). This was translated to a workable percentage of 75% for the tablets and 65-70% for the drops. The reduction is equivalent to a maximum dose of 30 mg/day up to age 65 years and 15 mg/day for 65 years and older. This is equivalent to 22 mg/day and 10 mg/day for the drops, which have a higher bioavailability.

Recommendation concerning pre-emptive genotyping, including justification of choices:
The Dutch Pharmacogenetics Working Group considers genotyping before starting citalopram to be potentially beneficial. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the Dutch Pharmacogenetics Working Group recommends adhering to the gene-drug guideline.
The clinical implication of the gene-drug interaction scores 1 out of the maximum of 10 points (with pre-emptive genotyping considered to be potentially beneficial for scores ranging from 0 to 2 points) (see also the clinical implication score tables at the end of this risk analysis):
No severe clinical effects were observed in users of citalopram with a variant phenotype. The maximum severity code was B corresponding to CTCAE grade 1. This results in a score of 0 out of the maximum of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (only points for CTCAE grade ≥ 3).
The lack of a 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 citalopram recommends a decreased maximum dose for CYP2C19 PM, but neither mentions CYP2C19 PM as a contra-indication for citalopram nor recommends pre-emptive genotyping. This results in 1 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (1 point for at least one genotype/phenotype mentioned in the SmPC, but not mentioned as a contra-indication and no recommendation to genotype).

The table below 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.

<table>
<tr><th>Source</th><th>Code</th><th>Effect</th><th>Comments</th></tr>
<tr><td>ref. 1
Kumar Y et al. CYP2C19 variation, not citalopram dose nor serum level, is associated with QTc prolongation.
J Psychopharmacol 2014;28:1143-8.
Pubmed PMID: 25122046.</td><td>3

IM: AA
IM+PM: A</td><td>75 patients were treated with citalopram 10-80 mg/day. Relevant co-medication was not excluded and the percentage of patients with relevant co-medication was lower for IM+PM patients than for EM patients (18% versus 52%) (S). However, co-medication with CYP2C19 substrates, inhibitors or inducers did not affect the results.

Genotyping:
- 58x EM
- 17x IM+PM (16x IM + 1x PM)

Results:
<table>
<tr><td colspan="2">QT_c interval versus EM (427.1 ms):</td></tr>
<tr><td>IM</td><td>+ 2.4% (NS, trend, p=0.066)</td></tr>
<tr><td>IM+PM</td><td>+ 3.0% (S)</td></tr>
<tr><td>PM</td><td>+ 13.2%</td></tr>
</table>
<table>
<tr><td>IM+PM versus EM:</td></tr>
<tr><td>no difference in:
- the median dose (NS)
- the percentage of patients with a dose exceeding 40 mg/day (NS)</td></tr>
</table>
NOTE: There was no association between the plasma concentration of citalopram and the QT_c interval (n = 42) (NS). There was also no association between the dose and the QT_c interval (n = 117) (NS).</td><td>Authors' conclusion:
'Of 75 citalopram patients, the EM group had significantly shorter QTc intervals than a combined IM+PM group. There was no statistical correlation between citalopram dose and QTc. QTc was not associated with citalopram serum level. Our findings suggest cytochrome P450 genotyping in select patients may be helpful to guide medication optimization while limiting harmful effects.'</td></tr>
<tr><td>ref. 2
Chen B et al. Estimation of CYP2D6*10 genotypes on citalopram disposition in Chinese subjects by popu-</td><td>4</td><td>23 healthy volunteers, selected for CYP2C19 genotype, received 2x single dose of 20 mg citalopram in a bio-equivalence study. Co-medication was excluded.

Genotyping:
- 9x EM</td><td>Authors' conclusion:
'CYP2C19 and CYP2D6 genotypes have impacts on the CL/F of citalopram.'</td></tr>
</table>

<table>
<tr>
<td>lation pharmacokinetic assay.
J Clin Pharm Ther 2013;38:504-11.
PubMed PMID: 23981149.

ref. 2, continuation</td>
<td>IM: AA</td>
<td>- 14x IM

Results:
<table><tr><td colspan="2">AUC versus EM (1376 ng.hour/mL):</td></tr><tr><td>IM</td><td>x 1.31 (NS)</td></tr></table>
<table><tr><td colspan="2">Clearance versus EM (15.3 L/hour):</td></tr><tr><td>IM</td><td>x 0.78 (NS, trend, p = 0.071)</td></tr></table>
N.B.: Alleles *2 and *3 were genotyped. Genotype *3 was not detected.</td>
<td>AUC citalopram versus EM:
IM: 131%</td>
</tr>
<tr>
<td>ref. 3
De Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients.
Pharmacogenomics J 2011;11:359-67.
PubMed PMID: 20531370.</td>
<td>3

UM: AA

IM: A

PM: AA</td>
<td>Routine therapeutic drug monitoring was performed for 338 patients on citalopram.
Genotyping:
- 233x EM (143x *1/*1, 90x *1/*17)
- 18x UM
- 81x IM (57x *1/*2, 24x *2/*17)
- 6x PM (*2/*2)
The citalopram dose was known in 223 patients (157x EM, 13x UM, 49x IM, 4x PM). The dose varied from 10-60 mg/day, with an average of 30 mg/day. Relevant co-medication was not excluded.
UM versus EM:
- the dose-corrected C_{ss} decreased by 26% (from 2.6 to 1.9 μg/L per mg) (NS)
- increase in the dose by 11% (from 30 mg to 33 mg/day) (NS)
- the MR citalopram/desmethylcitalopram decreased by 7.9% (from 2.6 to 2.4) (NS)
- factor 1.5 increase in the percentage of patients with plasma concentrations below the therapeutic range (30-130 μg/L) (from 11% to 17%) (NS)
- factor 0.44 decrease in the percentage of patients with plasma concentrations above the therapeutic range (30-130 μg/L) (from 14% to 6%) (NS)
IM versus EM:
- the dose-corrected C_{ss} increased by 39% (from 2.6 to 3.6 μg/L per mg) (S for *1/*2, NS for *2/*17)
- decrease in the dose by 4.0% (from 30 mg to 28 mg/day) (NS)
- increase in the MR citalopram/desmethylcitalopram by 20% (from 2.6 to 3.1) (S for *1/*2, NS for *2/*17)
- factor 0.66 decrease in the percentage of patients with plasma concentrations below the therapeutic range (30-130 μg/L) (from 11% to 7.4%) (NS)
- factor 1.3 increase in the percentage of patients with plasma concentrations above the therapeutic range (30-130 μg/L) (from 14% to 17%) (NS)
PM versus EM:
- the dose-corrected C_{ss} decreased by 6.3% (from 2.6 to 2.4 μg/L per mg) (NS)
- increase in the dose by 38% (from 30 mg to 41 mg/day) (NS)
- increase in the MR citalopram/desmethylcitalopram by 65% (from 2.6 to 4.3) (NS)
- NOTE: The direction of the change in MR (n=6) was as expected, but the opposite effect occurred for the dose-corrected C_{ss} and the dose (both n=4).</td>
<td>Authors' conclusion:
'This study confirms the increased activity of the CYP2C19*17 allele and shows increased metabolism of drugs that are metabolized by CYP2C19, including citalopram. However, the clinical relevance of CYP2C19*17 is probably limited for citalopram.'

C_{ss} citalopram versus EM:
UM: 74%
IM: 139%
PM: 94%</td>
</tr>
</table>

ref. 3, continuation		- decrease in the percentage of patients with plasma concentrations below the therapeutic range (30-130 µg/L) from 11% to 0% (NS) - factor 2.4 increase in the percentage of patients with plasma concentrations above the therapeutic range (30-130 µg/L) (from 14% to 33%) (NS) NOTE: Alleles *2 and *17 were genotyped	
ref. 4 Mrazek DA et al. CYP2C19 variation and citalopram response. Pharmacogenet Genomics 2011;2:1-9. PubMed PMID: 21192344.	3 UM: AA IM: AA IM+PM: B PM: AA#	Analysis of the data from 1,074 white patients without Latin-American, Spanish or Portuguese heritage from the same study by Peters et al., 2008. With regard to the tolerance, data were compared between the tolerant group (n=872) and the intolerant group (n=80). Patients who were possibly or probably intolerant were not included in this analysis. Similar results were obtained if patients who had been using citalopram for less than six weeks (tolerance and remission) or who were not therapy compliant (tolerance) were also included. Genotyping: - 867x EM (368x *1/*1, 499x *1/*17) - 60x UM - 298x IM (222x *1/null allele, 76x *17/null allele) - 28x PM General: - trend for increased probability of tolerance with higher predicted CYP2C19 activity (OR = 1.20; 95% CI: 1.00-1.44) (NS) - the *1 allele did not result in an increased probability of tolerance (OR = 1.08; 95% CI: 0.77-1.52) (NS) - no difference in the probability of remission between the phenotype groups (NS) - decrease in the probability of remission with the predicted CYP2C19 activity for tolerant patients (S). However, for each of the individual groups, the 95% CIs overlap with those of *1/*1 and *1/*17 (NS). - the *1 allele did not result in an increased probability of remission in all patients (OR = 1.17; 95% CI: 0.98-1.41) and in tolerant patients (OR = 1.19; 95% CI: 0.97-1.45) (NS) - there was no association between the final dose and the genotype (NS) - for two smaller groups (196 patients of Latin-American heritage and 233 Afro-American patients), there was no increase in probability of tolerance with higher predicted CYP2C19 activity (NS) null alleles: - reduced probability of tolerance for *2 (OR = 0.60; 95% CI: 0.39-0.91) (S) - trend towards reduced probability of tolerance for all null alleles combined (OR = 0.66; 95% CI: 0.43-1.00) (NS) - no difference in remission in all patients and in tolerant patients for *2 and for all null alleles combined (NS) - a post-hoc analysis revealed that tolerant PM had a greater probability of remission (S).	Authors' conclusion: 'Despite several limitations including the lack of serum drug levels, this study demonstrated that variations in CYP2C19 were associated with tolerance and remission in a large sample of white non-Hispanic patients treated with citalopram.'

ref. 4, continuation		For PM, the probability of remission was elevated by 48% compared to EM (from 59% to 87%). (however, lower remission percentages were found for IM than for EM). *17 allele: - no increase in the probability of tolerance (NS) - trend towards a decrease in the probability of remission in all patients (OR = 0.84; 95% CI: 0.69-1.04) and in tolerant patients (OR = 0.80; 95% CI: 0.63-1.00)) (NS) N.B.: genotyping was performed for *2 to *8 and *17.	
ref. 5 Fudio S et al. Evaluation of the influence of sex and CYP2C19 and CYP2D6 polymorphisms in the disposition of citalopram. Eur J Pharmacol 2010;25:200-4. PubMed PMID: 19840783.	3 IM: A PM: A	A total of 35 healthy volunteers received a single dose of citalopram 20 mg. No medication was used from two weeks prior to the study. This was a cross-over study involving two citalopram tablets. The authors did not provide raw data, only data predicted using a mixed linear model for repeated measurements, which included citalopram formulation, period, order, gender and CYP2C19 and CYP2D6 genotype. Genotyping: - 26x EM - 7x IM (*1/*2) - 2x PM (*2/*2) IM versus EM: - dose-corrected and body weight-corrected AUC increased by 44% (from 2154.4 to 3112.0 ng.hour/mL per mg/kg) (S for the trend PM, IM, EM) - weight-corrected Cl_{or} decreased by 5.8% (from 6.77 to 6.38 mL/min per kg) (S for the trend PM, IM, EM) PM versus EM: - dose-corrected and body weight-corrected AUC increased by 119% (from 2154.4 to 4709.1 ng.hour/mL per mg/kg) (S for the trend PM, IM, EM) - weight-corrected Cl_{or} decreased by 35% (from 6.77 to 4.39 mL/min per kg) (S for the trend PM, IM, EM) N.B.: genotyping was performed for *2 and *3.	Authors' conclusion: 'In conclusion, we demonstrate the influence of CYP2C19 and CYP2D6 in the disposition of citalopram, and we suggest that the influence of CYP2D6 is more probable in volunteers with at least one defective allele of CYP2C19.' AUC citalopram versus EM: IM: 144% PM: 219%
ref. 6 Hilli J et al. MAO-A and COMT genotypes as possible regulators of perinatal serotonergic symptoms after in utero exposure to SSRIs. Eur Neuropsychopharmacol 2009;19:363-70. PubMed PMID: 19223155.	3 IM+PM: AA	Ten newborn babies born to women who used citalopram 20-40 mg/day during the pregnancy were genotyped. There was no relevant co-medication (levothyroxine in one patient and alprazolam or lorazepam as needed in four patients). The mother's genotype was not known. Genotyping: - 5x EM - 4x IM - 1x PM (IM+PM) versus EM: - no difference in the severity of serotonergic symptoms in the newborns (NS) - the plasma concentration of citalopram decreased by 36% (from 61.6 nmol/L to 39.4 nmol/L) (NS) - increase in the ratio desmethylcitalopram/	Authors' conclusion: 'The infant CYP2C19 genotype did not affect the extent of the exposure to citalopram or the serotonergic symptom score. Furthermore, it has been reported earlier that the citalopram concentrations did not show any significant correlations with the serotonergic symptom scores in these infants. …… It should also be remembered that the mother's genotype of drug meta-

ref. 6, continuation		citalopram by 15% (from 0.47 to 0.54) (NS) N.B.: genotyping was performed for *2.	bolizing enzymes is likely to be a more important determinant of the *in utero* exposure to SSRIs.'
ref. 7 Peters EJ et al. Pharmacokinetic genes do not influence response or tolerance to citalopram in the STAR*D sample. PLoS ONE 2008;3:e1872.	3 IM + PM: AA *1/*17 + *2/*17 + *3/*17 + UM: AA PM: AA	A case-control study examined the association between CYP2C19 polymorphisms and citalopram response and tolerance. Any associations that were found were validated in a second study in a second set of patients. Non-responders were compared to responders (≥ 50% reduction in symptoms), to patients who achieved remission (virtually complete reduction of symptoms) and to specific responders (the response that occurred remained present throughout the study period, in order to rule out placebo responses). In addition to this, patients who were tolerant or intolerant to citalopram were compared to each other. Caucasian and Afro-American patients were compared to each other. The number of patients per group varied from 51-554 for Caucasians and from 9-89 for Afro-Americans. Patients received citalopram 20-60 mg/day for 12 weeks. The average dose at the end of the study was 45.5 mg/day. Relevant co-medication was not excluded. *2 versus no *2: - The first study found a significant difference in frequency between the tolerant group and the non-tolerant group. However, this was not the case in the validation study. *3 versus no *3: - No significant differences. *17 versus no *17: - No significant differences. PM versus EM + IM + UM: - No association with response or tolerance. - No significantly lower average dose at the end of the study. - No significant effect on premature withdrawal from the study.	Authors' conclusion: 'Thus, at least for citalopram, it may be premature to advocate pharmacokinetic gene analysis for dose adjustment or clinical decision making.'
ref. 8 Yin OQ et al. Phenotype-genotype relationship and clinical effects of citalopram in Chinese patients. J Clin Psychopharmacol 2006;26:367-72.	4 IM: A PM: A	A total of 53 Chinese patients, 21x EM, 25x IM (24x *1/*2, 1x *1/*3), 7x PM (3x *2/*2, 2x *2/*3, 2x *3/*3), received citalopram 10-60 mg/day for ≥2 weeks, co-medication: no inducers or inhibitors of CYP2C19 were permitted, but CYP2C19 substrates were; - no significant difference in the occurrence of adverse events between genotypes, EM:IM:PM = 89.2:93.3:100.1 - significant relationship between occurrence of adverse events and the oral clearance of citalopram predicted using population kinetics.	
ref. 9 Rudberg I et al. Heterozygous mutation in CYP2C19 significantly increases the concentrations/dose ratio of racemic	4 IM: A	A total of 40 patients, 23x EM and 17x IM (*1/*2), treated with citalopram (EM 35 mg/day, IM 34 mg/day), no CYP2C19 inhibitors or inducers as co-medication; IM versus EM: - sign. increase in conc[a] from 4.9 to 8.0 (S by 63%). - sign. increase in MR[a] by 81%.	Authors' conclusion: 'Citalopram is a well-tolerated drug, but it can not be ruled out that the approximately 2-fold increase in C/D ratio among HEMs is of possible therapeutic importance. However,

citalopram and escitalopram (S-citalopram). Ther Drug Monitor 2006;28:102-5. **ref. 9, continuation**			the use of equal daily doses in the EM and HEM groups suggests that the dose reductions compensating for the reduced metabolism among HEMs are not performed in clinical practice.' IM: conc increased up to 163% versus EM.
ref. 10 Herrlin K et al. Metabolism of citalopram enantiomers in CYP2C19/CYP2D6 phenotyped panels of healthy Swedes. Br J Clin Pharmacol 2003;56:415-21.	4 PM: A	Nineteen Swedish healthy volunteers, 7x PM for CYP2C19 (phenotyped with mephenytoin for CYP2C19 and debrisoquine for CYP2D6) received citalopram 20 mg/day (1 person was PM for both 2C19 and 2D6 and received 10 mg/day) for 7 days, no relevant co-medication; 2C19PM: - AUC racemate increased from 1398 to 1669 nM/h (by 19%, significance unknown) - AUC of S-CT increased from 530 to 830 nM/h (S by 57%). - no significant difference for AUC of R-CT. - AUC of S-desmethyl-CT decreased from 208 to 182 nM/h (NS by 13%) and for R-desmethyl-CT from 233 to 172 nM/h (NS by 26%). - PM for both 2C19 and 2D6 developed adverse events, possibly serotonin syndrome, withdrew from study on day 5. The t½ for citalopram is 95 hours N.B.: genotypes not listed.	PM: AUC increased by up to 119% versus EM+IM.
ref. 11 Yu BN et al. Pharmacokinetics of citalopram in relation to genetic polymorphism of CYP2C19. Drug Metab Dispos 2003;31:1255-9.	3 PM: A IM: A	Thirteen Chinese healthy volunteers, 4x EM (*1/*1), 4x IM (*1/*2), 5x PM (*2/*2 or *2/*3), received a single dose of 40 mg citalopram, no relevant co-medication; sign. effect of CYP2C19 genotype on N-demethylation of citalopram. - PM: increase in the AUC CT versus EM from 1677.5 to 2132.5 µg.h/L (S by 27%), decrease in Cl_{or} from 0.41 to 0.31 L/h/kg (S by 24%), increase in t½ CT from 35.6 to 39.1 hours (S by 10%), decrease in AUC N-desmethyl-CT from 855.4 to 516.7 µg.h/L (S by 40%). - IM: compared to EM, none of the kinetic parameters for CT and N-desmethyl-CT changed significantly. Increase in AUC CT from 1677.5 to 1774.2 µg.h/L (NS by 5.8%), decrease in Cl_{or} from 0.41 to 0.36 L/h/kg (NS by 12%). N.B.: study was performed with and without addition of CYP3A4 inhibitor (troleandomycin). For the EMs CYP3A4 had no effect, for the PMs the addition of a CYP3A4 inhibitor resulted in a significantly higher AUC of CT and N-desmethyl-CT	PM: AUC increased by up to 127% and Cl_{or} decreased by up to 76% versus EM. IM: AUC increased by up to 106% and Cl_{or} decreased by up to 88% versus EM.
ref. 12 Baumann P et al. A double-blind, placebo-controlled study of citalopram with and without lithium in the treat-	4	A total of 69 patients, 6x CYP2C19 PM, 3x CYP2D6 PM (phenotyped with mephenytoin for CYP2C19 and debrisoquine for CYP2D6) received citalopram 40-60 mg/day for 4 weeks, no relevant co-medication. After four weeks there were 45 responders and 24	Authors' conclusion: 'The fact that the metabolism of citalopram and N-desmethylcitalopram is affected in patients with a genetic deficiency of

ment of therapy-resistant depressive patients: a clinical, pharmacokinetic, and pharmacogenetic investigation. J Clin Psychopharmacol 1996;16:307-14.	PM: A	non-responders. Of the six CYP2C19 PMs, three were responders and three were non-responders. - CYP2C19 PM: increase in the plasma conc[a] CT versus EM from 2.22 to 3.64 µg/L/.mg dose (S by 64%), decrease in N-desmethyl-CT from 1.05 to 0.64 µg/L.mg dose (S by 39%), decrease in didesmethyl-CT from 0.19 to 0.11 µg/L.g dose (S by 42%).	CYP2D6 or CYP2C19 does not seem to be an important factor for adverse effects. PM: concentration increased by up to 164% versus EM+IM.
ref. 13 Sindrup SH et al. Pharmacokinetics of citalopram in relation to the sparteine and the mephenytoin oxidation polymorphisms. Ther Drug Monit 1993;15:11-7.	4 PM: A	A total of 24 healthy volunteers, 18x EM (of which 6 CYP2D6 PM), 6x PM received 40 mg citalopram for 10 days, co-medication unknown - PM: increase in the AUC CT versus EM (for CYP2C19 and 2D6) from 4.588 to 8.145 nM.hr (S by 76%), decrease in clearance from 27.3 to 15.2 L/h (S by 44%), increase in t½ from 30 to 42 hours (S by 40%), decrease in AUC N-desmethyl-CT from 1.768 to 1.475 nM.hr (NS by 17%), decrease in AUC didesmethyl-CT from 370 to 153 nM.hr (NS by 59%). Adverse events: no difference between the various genotypes. The AUC and t½ of CT are increased in the PMs for CYP2D6, but not to the same extent as for CYP2C19 PMs.	PM: AUC increased by up to 176% and Cl_{or} decreased by up to 56% versus EM+IM.
ref. 14 SmPC Cipramil (citalopram) 01-04-17.	PM: A	Dose: For the first two weeks of the treatment, an initial dose of 10 mg per day is recommended for patients who are known to have a slow CYP2C19 metabolism. Depending on individual patient response, the dose may be increased to a maximum of 20 mg per day. Pharmacokinetic properties: In patients with a known abnormality in the metabolism of the CYP2C19 enzyme, an initial dose of 10 mg is recommended as a precaution.	Maximum dose versus EM: PM: 50%
ref. 15 SmPC Celexa (citalopram), USA, 04-01-17.	PM: A	Pharmacokinetics: In CYP2C19 poor metabolizers, citalopram steady state Cmax and AUC was increased by 68% and 107%, respectively. Celexa 20 mg/day is the maximum recommended dose in CYP2C19 poor metabolizers due to the risk of QT prolongation. Warning: QT-prolongation and Torsades de Pointes: The maximum dose should be limited to 20 mg/day in patients who are CYP2C19 poor metabolizers, since higher citalopram exposures would be expected. Dose: 20 mg/day is the maximum recommended dose for CYP2C19 poor metabolizers.	AUC citalopram versus EM: PM: 207%

[a] Corrected for dose.

Risk group	IM with CYP2D6 inhibitor

Comments:

- For the period after 2011, clinical studies with outcome measures other than QT elongation were only included if n > 100.
  Kinetic studies have only been included if the outcome measures were determined separately for citalopram and escitalopram. In addition to this, kinetic studies were only included if the (dose-corrected) exposure to citalopram was determined.
- The S-enantiomer of citalopram is primarily responsible for the anti-depressant and anxiolytic effect.

- The reference Rudberg, 2006 and Herrlin, 2003 show that CYP2C19 plays a greater role in S-citalopram metabolism than in R-citalopram metabolism. Carlsson B et al. Enantioselective analysis of citalopram and metabolites in adolescents. However, Ther Drug Monit 2001;23:658-64 found no differences between *1/*1 and *1/*2 patients in S-/R-enantiomer ratio for both CT and N-desmethyl-CT.
- The authors of Rudberg, 2006 noted that the quantitative effect of CYP2C19 genotype may increase at higher doses/concentrations, because CYP2C19 has low affinity but high capacity for N-demethylation of citalopram.
- In patients with intoxication symptoms, the plasma concentration of citalopram was ≥ 0.21 mg/L (Jimmink A et al. Ther Drug Monit 2008;30:365-71). De Vos, 2010 stated that therapeutic plasma concentrations of citalopram range between 30 and 130 µg/L.
- 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 CYP2C19 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 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 individuals' 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 CYP-2C19-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.
    Significantly lower depressive symptoms (measured using the Center of Epidemiologic Studies Depression (CES-D) scale) were found for PM than for *1/*1 in a group of 1,472 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). The difference was only observed in patients younger than 73 years and in men. The difference was of the same order of magnitude as that between non-users and antidepressant users. The authors stated that CYP2C19 polymorphisms may influence depressive symptoms in adult Europeans.
- Existing guidelines:
  Hicks JK et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. Clin Pharmacol Ther 2015;98: 127-34. PubMed PMID: 25974703.
  CPIC uses the same definitions of IM and PM as we do. However, CPIC uses different definitions for EM (*1/*1) and UM (*1/*17 or *17/*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 states that *1/*17+UM patients have lower exposure to citalopram and escitalopram than *1/*1

patients (Huezo-Diaz 2012, Hodgson 2014, Rudberg 2008 (all articles about escitalopram)). This leads to an increased risk of failure of the therapy. There are insufficient data to calculate an adjusted initial dose. An alternative SSRI not predominantly metabolised by CYP2C19 may therefore be an option, provided that it is suitable as part of the patient's medication regimen and other clinical considerations. CPIC classifies this recommendation as "moderate" as there can be clinically significant differences between *1/*17 and UM. The articles by Bishop 2015 (indication autism spectrum disorder) and Brasch-Andersen 2011 (indication neuropathic pain) have not been used to support the recommendation. Neither study found a genotype effect on the efficacy of escitalopram. Consistent with Hodgson 2014, Bishop 2015 also did not find a genotype effect on dose. The dose was guided by effect in both studies.
IM patients may have increased plasma concentrations. Dose extrapolations suggest that minimal dose adjustments are needed for IM (Stingl JC et al. Mol Psychiatry 2013;18:273-87). CPIC classifies the recommendation to initiate treatment with the standard initial dose as "strong".
Increased plasma concentrations have been observed in PM patients, which can increase the risk of adverse events (Chen 2013, Fudio 2010, Noehr-Jensen 2009 and Rudberg 2008). In order to prevent potential adverse events, alternative SSRIs not predominantly metabolised by CYP2C19 should be considered. If citalopram or escitalopram are preferred, an initial dose reduction of 50% should be considered (Stingl 2013). The FDA recommends a 50% dose reduction for citalopram due to the risk of QT prolongation. This FDA recommendation is not relevant for escitalopram. There are only very few data on the relationship between SSRI concentrations and therapeutic effect or tolerability. The CPIC classified the recommendation as "moderate", due to the likely risk of arrhythmias in combination with the specific dose recommendations given by the FDA.
The recommendations are as follows:
- *1/*17 and UM: consider an alternative that is not predominantly metabolised by CYP2C19.
- IM: no action needed.
- PM: consider decreasing the dose to 50% of the standard initial dose and guide the dose by effect or choose an alternative that is not predominantly metabolised by CYP2C19.

CYP2C19 activity may be higher in children than in adults. The recommendations above should therefore be followed with caution in children and children should be closely monitored.
On 3-4-2018, there was not a more recent version of the recommendations present on the PharmGKB- and on the CPIC-site.

Date of literature search: 29 March 2018.

	Phenotype	Code	Gene-drug interaction	Action	Date
Project group decision	IM	4 A	Yes	Yes	14 May 2018
	PM	4 A	Yes	Yes	
	UM	3 AA	Yes	No	

Mechanism:
Citalopram is primarily metabolised by CYP2C19 and to a lesser extent by CYP3A4 to N-desmethylcitalopram. Although desmethylcitalopram has anti-depressant activity, the activity is low and not clinically relevant at the standard citalopram dose. N-desmethylcitalopram is converted by CYP2D6 to didesmethylcitalopram.
The upper limit of the therapeutic range of citalopram is 400 ng/mL.

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+	1+
Corresponding Clinical Implication Score:		Potentially beneficial