CYP2C19: sertraline 2008 to 2010

AUC = area under the concentration-time curve, Cl_{or} = oral clearance, C_{ss} = plasma concentration in steady state, EM = extensive metaboliser (*1/*1, *1/*17) (normal CYP2C19 enzyme activity), IM = intermediate metaboliser (*1/*2, *1/*3, *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), S = significant, SmPC = summary of product characteristics, $t_{1/2}$ = half-life, UM = ultrarapid 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 sertraline to the active metabolite desmethylsertraline. CYP2C19 may also play an important role in desmethylsertraline metabolism. Studies have shown an increase in the concentration of sertraline for genotype groups associated with reduced CYP2C19 activity (intermediate and poor metabolisers (IM and PM)).

UM: One study including 5 UM patients did not find a significant effect of UM on dose-corrected sertraline plasma concentrations (Rudberg 2008). One study including 3 UM patients did not find a difference in side effects and no significant difference in response between the genotype groups (Brandl 2014). As there is no evidence for a kinetic or clinical effect of UM, no action is needed for this gene-drug interaction (yes/no-interaction).

IM+PM: One study including 29 IM and 5 PM patients found that repeated dosing led to a significant increase in dose-corrected sertraline plasma concentrations in IM and PM patients (Rudberg 2008). A study with 8 healthy IM found the same after a single dose (Saiz-Rodríguez 2018). There is limited evidence for an increased risk of side effects in PM patients (Grasmader 2004 (2 PM) and Wang 2001 (6 PM)). The only study determining the risk of side effects separately for IM, found no increase for 8 healthy IM after a single dose (Saiz-Rodríguez 2018). AlOlaby 2017 found a better clinical outcome of treating children with fragile X syndrome with sertraline for IM+PM. However, this indication has not been licenced for sertraline, so the better results for IM+PM might be due to a suboptimal dose for EM. The increase in concentration is high compared to the therapeutic range for PM patients (factor 2.9 versus factor 6). This is why a decision was made to recommend a decrease in the maximum dose for PM patients (yes/yes-interaction). However, the increase in exposure is low compared to the therapeutic range for IM patients (factor 1.4-1.5 versus factor 6). Combined with the lack of studies or case reports showing an increase of adverse events in IM, it was decided that there was not enough evidence to recommend an adjustment of therapy for IM patients (yes/no-interaction).

You can find an 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 text via your pharmacy or physician information system.

Substantiation for the dose recommendation for PM patients is provided below.

Justification of dose recommendation

Dose adjustments have been calculated on the basis of changes in steady state plasma concentrations or AUC of sertraline. There was only one article that compared sertraline plasma concentrations in PM to those in EM (Rudberg 2008, 121 patients, including 5 PM).

PM: The calculated dose adjustment is a dose reduction to 34% of the standard dose. This was translated to 37.5% to be more achievable in clinical practice.
As the lowest strength sertraline tablet contains 25 mg and as this is usually the initial dose for children and for some indications in adults, the recommendation for dose decrease is limited to the maximum dose.

Recommendation concerning pre-emptive genotyping, including justification of choices:
The Dutch Pharmacogenetics Working Group considers genotyping before starting sertraline 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 sertraline with a variant phenotype. The maximum severity code was C corresponding to CTCAE grade 2. 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 sertraline indicates that the sertraline plasma concentration in CYP2C19 PM is about 1.5-fold the plasma concentration in CYP2C19 EM, but neither mentions CYP2C19 PM as a contra-indication for sertraline 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
Saiz-Rodríguez M et al.
Effect of polymorphisms on the pharmacokinetics, pharmacodynamics and safety of sertraline in healthy volunteers.
Basic Clin Pharmacol Toxicol 2018;122:501-511.
PubMed PMID: 29136336.</td>
<td>3

IM: A

(*1/*17 + *2/*17): A</td>
<td>46 healthy volunteers received a single dose of sertraline 100 mg on two separate occasions.
Adverse drug reactions were defined as adverse events that were definitely, probably or possibly caused by sertraline.
No severe adverse events occurred. 73.9% of the volunteers experienced at least one adverse drug reaction. The most frequent were insomnia (43.5%), nausea/vomiting (34.8%) and headache (30.4%).
Co-medication and smoking were excluded.

Genotyping:
- 28x *1/*1
- 9x IM
- 9x *1/*17+*2/*17 (7x *1/*17, 2x *2/*17)

Results:
<table>
<tr><td colspan="4">Results compared to *1/*1:</td></tr>
<tr><td></td><td>IM</td><td>*1/*17 + *2/*17</td><td>value for *1/*1</td></tr>
<tr><td rowspan="2">% of patients with at least 1 adverse drug reaction</td><td colspan="2">NS for IM versus *1/*1 versus *1/*17+*2/*17</td><td rowspan="2">75.9%</td></tr>
<tr><td colspan="2">There was a tendency of more adverse drug reactions in individuals with higher AUC (CYP2C19 IM and CYP2B6 T/T) (NS).The percentage of CYP2C19 IM with at least one adverse drug reaction was 1.15-fold that of *1/*1 (87.5%).</td></tr>
<tr><td>AUC sertraline</td><td>x 1.38 (NS, but S for IM versus EM+ *2/*17)</td><td>x 0.73 (S, both in univariate and multivariate analysis and also after excluding the *2/*17 patients from the analysis)</td><td>862.9 ng/hr.ml</td></tr>
</table>
</td>
<td>Authors’ conclusion: “Polymorphisms in CYP2C19 and CYP2B6 genes influenced sertraline pharmacokinetics, with a greater effect of CYP2C19. …. There was a tendency to present more adverse drug reactions in women and individuals with higher AUC of sertraline, such as CYP2C19 intermediate metabolizers and CYP2B6 G516T T/T individuals.”

AUC sertraline versus *1/*1:
IM: 138%</td>
</tr>
</table>

<table>
<tr><td>ref. 1, continuation</td><td></td><td>NOTE: Genotyping was for *2, *3 and *17. These are the most important gene variants in this Spanish population.</td><td></td></tr>
<tr><td>ref. 2
AlOlaby RR et al. Molecular biomarkers predictive of sertraline treatment response in young children with fragile X syndrome. Brain Dev 2017;39:483-492. PubMed PMID: 28242040.</td><td>3

IM+PM: AA#

(*1/*17 + UM): AA</td><td>In a double blind clinical trial, 19 children with fragile X syndrome, 2 to 6 years of age, receiving sertraline were compared to 24 children receiving placebo. Sertraline was administered in liquid form in a dose of 2.5 mg/day for patients aged 2 or 3 years and 5.0 mg/day for patients aged 4 years to 5 years and 8 months. The duration of the clinical trial was 6 months.
Fragile X syndrome is characterised by an altered brain development resulting in significant behavioural, cognitive, and emotional problems. Deficits in serotonin synthesis in young children resulting in impaired synaptogenesis and postnatal brain development, are believed to play a role in disease development.
Primary outcome measures were the Mullen Scales of Early Learning (MSEL) expressive language raw score and expressive language standard score, and the Clinical Global Impression Scale-Improvement (CGI-I). The CGI-I is a 7-point scale varying from 1 = very much improved since the initiation of treatment to 7 = very much worse since the initiation of treatment.
Associations with CYP2C19 genotype were investigated by regression analysis with genotype, treatment, genotype by treatment interaction, baseline score (baseline score for severity for CGI), molecular category (fragile X syndrome caused by full mutation versus mosaic), and gender.
Relevant co-medication was not excluded. In addition, most but not all children also received a non-pharmacological intervention.

Genotyping:
sertraline group
- 8x (6x *1/*1, 2x *17/null)
- 6x IM+PM (5x IM, 1x PM)
- 5x *1/*17+UM
placebo group
- 11x *1/*1+*17/null (10x *1/*1, 1x *17/null)
- 5x IM+PM (4x IM, 1x PM)
- 8x *1/*17+UM

Results:
<table>
<tr><td colspan="3">Efficacy results compared to *1/*1+*17/null:</td></tr>
<tr><td></td><td>IM+PM</td><td>*1/*17+UM</td></tr>
<tr><td>CGI-I</td><td>A higher percentage was very much improved in the sertraline group compared to the placebo group (S).</td><td>NS</td></tr>
<tr><td></td><td colspan="2">Linear regression showed an association of the CYP2C19 phenotype with the CGI-I (S).</td></tr>
<tr><td>Sensory Processing Measure – Preschool Home Form – social participa-</td><td>No significant difference between sertraline and placebo, while there was a significant difference for *1/*1+*17/null.</td><td>No significant difference between sertraline and placebo, while there was a significant difference for *1/*1+*17/null.</td></tr>
</table></td><td>Authors’ conclusion: “Polymorphisms in the MAOA, Cytochrome P450 2C19 and 2D6, and in the 5-HTTLPR gene showed a significant correlation with some of the secondary measures included in this study. This study shows that polymorphisms of genes involved in the serotonergic pathway could play a potential role in predicting response to sertraline treatment in young children with fragile X syndrome.”</td></tr>
</table>

<table>
<tr><td>ref. 2, continuation</td><td></td><td>
<table>
<tr><td>tion raw score</td><td>Linear regression showed no association of the CYP2C19 phenotype with the social participation raw score (NS).</td></tr>
<tr><td colspan="2">No association with the CYP2C19 phenotype was found for the following response parameters:
- MSEL expressive language raw score
- MSEL composite score
- MSEL receptive language raw score
- MSEL visual reception raw score
- MSEL fine motor raw score
- MSEL visual reception age equivalent score
- MSEL fine motor age equivalent score
- MSEL cognitive T score (cognitive standard score)</td></tr>
</table>

NOTE 1: Genotyping was for *2, *3 and *17. These are the most important gene variants in this population from the USA.

NOTE 2: The authors do not provide the definitions of the CYP2C19 phenotypes mentioned in the article. As a consequence, an educated guess had to be made regarding these definitions.
</td><td></td></tr>
<tr><td>ref. 3
Yuce-Artun N et al. Influence of CYP2B6 and CYP2C19 polymorphisms on sertraline metabolism in major depression patients. Int J Clin Pharm 2016;38:388-94. PubMed PMID: 26830411.</td><td>4

PM: AA
IM: AA</td><td>50 patients were treated with sertraline (mean 58 mg/day). Co-medication influencing CYP2C19 or CYP2B6 was excluded.

Genotyping:
- 22x *1/*1
- 11x *1/*17
- 12x *1/*2
- 4x *17/*2
- 1x PM

Results:
<table>
<tr><td>PM versus *1/*2 versus *17/*2 versus *1/*1 versus *1/*17:</td></tr>
<tr><td>No difference in:
- Dose-corrected C_{ss} of sertraline (NS)
- Dose-corrected C_{ss} of desmethylsertraline (NS)
- Desmethylsertraline/sertraline metabolic ratio (NS)</td></tr>
<tr><td>The article does not contain data by genotype group.
The authors consider *17/*2 to be a genotype with normal activity.</td></tr>
</table>

NOTE: Alleles *2 and *17 were genotyped.</td><td>Authors’ conclusion: “We did not find any correlation between CYP2C19 genotype and serum concentrations of SERT and DSERT in MDD patients. …. Low frequencies of the CYP2C19 variant alleles and deficient genotypes might be the reason for not observing any differences between wild-type and variant allele carriers regarding to SERT plasma concentrations.”</td></tr>
<tr><td>ref. 4
Brandl EJ et al. Influence of CYP2D6 and CYP2C19 gene variants on antidepressant response in obsessive-compulsive disorder. Pharmacogenomics J 2014;14:176-81. PubMed PMID: 23545896.</td><td>3</td><td>64 patients with obsessive-compulsive disorder were treated with sertraline at a dose of 100 mg/day or higher for more than 10 weeks. Response and side effects were assessed by patient interviews some time after treatment discontinuation. Response was measured using an OCD-adjusted CGI Improvement scale. Patients who showed a minimal improvement on this scale were included in the group of the non-responders. Patients with mild side effects were included in the group without significant side effects. Co-medication was not excluded.

Genotyping (calculated on the basis of the percentage distribution):</td><td>Authors’ conclusion: “There were nonsignificant trends for association of CYP2D6 metaboliser status with response to fluoxetine and of CYP2C19 metaboliser status with response to sertraline (P=0.064).”</td></tr>
</table>

ref. 4, continuation	PM: AA IM: AA UM: AA	- 47x EM+*17/*2 - 12x IM (*1/*2 and *1/*3) - 2x PM - 3x UM Results: PM versus IM versus (EM+*17/*2) versus UM: - Trend towards an association with response (NS; p = 0.064) - No difference in side effects (NS) NOTE: Alleles *2, *3 and *17 were genotyped.	
ref. 5 Rudberg I et al. Serum concentrations of sertraline and N-desmethylsertraline in relation to CYP2C19 genotype in psychiatric patients. Eur J Clin Pharmacol 2008;64:1181-8.	4 IM: A PM: A UM: AA	121 patients (82x EM (42x *1/*1, 40x *1/*17), 29x IM (22x *1/null allele, 7x *17/null allele), 5x PM, 5x UM) who were treated with sertraline. Relevant co-medication was excluded. *1/null allele versus *1/*1: - Sertraline C_{ss}[a] increased by 44% (from 0.62 to 0.89 nM/mg) (S) - Desmethylsertraline C_{ss}[a] increased by 92% (from 1.3 to 2.5 nM/mg) (S) *17/null allele versus *1/*1: - Sertraline C_{ss}[a] increased by 94% (from 0.62 to 1.2 nM/mg) (S) - Desmethylsertraline C_{ss}[a] increased by 85% (from 1.3 to 2.4 nM/mg) (S) PM versus *1/*1: - Sertraline C_{ss}[a] increased by 206% (from 0.62 to 1.9 nM/mg) (S) - Desmethylsertraline C_{ss}[a] increased by 362% (from 1.3 to 6.0 nM/mg) (S) UM versus *1/*1: - Sertraline C_{ss}[a] decreased by 1.6% (from 0.62 to 0.61 nM/mg) (NS) - Desmethylsertraline C_{ss}[a] increased by 69% (from 1.3 to 2.2 nM/mg) (NS) *1/*17 versus *1/*1: - Sertraline C_{ss}[a] increased by 10% (from 0.62 to 0.68 nM/mg) (NS) - Desmethylsertraline C_{ss}[a] increased by 23% (from 1.3 to 1.6 nM/mg) (NS) IM versus EM: - Sertraline C_{ss}[a] increased by 49% (from 0.65 to 0.96 nM/mg) (S) - Desmethylsertraline C_{ss}[a] increased by 71% (from 1.4 to 2.5 nM/mg) (S) - Sertraline+desmethylsertraline C_{ss}[a] increased by 64% (from 2.1 to 3.4 nM/mg) (S) PM versus EM: - Sertraline C_{ss}[a] increased by 193% (from 0.65 to 1.9 nM/mg) (S) - Desmethylsertraline C_{ss}[a] increased by 315% (from 1.4 to 6.0 nM/mg) (S) - Sertraline + desmethylsertraline C_{ss}[a] increased by 277% (from 2.1 to 7.9 nM/mg) (S) UM versus EM: - Sertraline C_{ss}[a] decreased by 6% (from 0.65 to 0.61 nM/mg) (NS) - Desmethylsertraline C_{ss}[a] increased by 52% (from 1.4 to 2.2 nM/mg) (NS) - Sertraline + desmethylsertraline C_{ss}[a] increased by 34%	Authors' conclusion: "The significantly higher serum concentrations associated with alleles encoding defective CYP2C19 metabolism might be of relevance for the clinical outcome of sertraline treatment." C_{ss} sertraline versus EM: IM: 149% PM: 293% UM: 94%

ref. 5, continuation		(from 2.1 to 2.8 nM/mg) (NS) NOTE: Alleles *2 to *5 and *17 were genotyped.	
ref. 6 Grasmader K et al. Impact of polymorphisms of cytochrome-P450 isoenzymes 2C9, 2C19 and 2D6 on plasma concentrations and clinical effects of antidepressants in a naturalistic clinical setting. Eur J Clin Pharmacol 2004;60:329-36.	3 PM: C	136 patients on antidepressants, including 14 on sertraline (dose not known) were genotyped. The 14 patients on sertraline included 2 PM patients and 12 either IM or EM patients. Relevant co-medication was not excluded. The mean dose-corrected sertraline C_{ss} was 0.41 ng/mL per mg dosed sertraline. The corrected plasma concentrations of the two PM patients were 36% and 188% higher than the median respectively. The PM patient with the lowest plasma concentration had relevant side effects.	
ref. 7 Wang JH et al. Pharmacokinetics of sertraline in relation to genetic polymorphism of CYP2C19. Clin Pharmacol Ther 2001;70:42-7.	3 PM: C IM: A	12 healthy volunteers (3x EM, 3x IM (2x *1/*2, 1x *1/*3), 6x PM (5x *2/*2, 1x *2/*3)) received a single dose of 100 mg sertraline. PM versus EM+IM: - The sertraline $AUC_{0-\infty}$ increased from 697.6 to 983.6 µg.hour/L (S by 41%) - The sertraline $t_{1/2}$ increased from 23.5 to 35.5 hours (S by 51%) - The sertraline Cl_{cr} decreased from 148.4 to 105.3 L/hour (S by 29%) - The desmethylsertraline $AUC_{0\text{-}144\ hours}$ decreased from 972.1 to 627.6 µg.hour/L (S by 35%) Contrary to sertraline, the desmethylsertraline $AUC_{0-\infty}$ is not equal to the $AUC_{0\text{-}144\ hours}$. - Two PM patients had various serious gastrointestinal side effects (including nausea, vomiting and diarrhoea) and various CNS symptoms (dry mouth, dizziness) 2 hours after administration of sertraline. IM versus EM: - Difference in sertraline Cl_{or} and $t_{1/2}$ (data not included in article) - No difference in sertraline AUC (data not included in article)	Authors' conclusion: "Thus poor metabolisers appear to be at increased risk for accumulation of sertraline and the possible development of sertraline-associated toxicity. Therefore, when sertraline is used clinically for the treatment of depression and obsessive-compulsive disorder, it is necessary to properly decrease its clinical dose for patients who are poor metabolisers of CYP2C19."
ref. 8 SmPC Zoloft (sertraline) 21-02-2018.	0 PM: A	<u>Pharmacokinetics</u>: Sertraline plasma concentrations were enhanced by about 50% in poor metabolisers of CYP2C19 compared to extensive metabolisers. The clinical significance of the increased plasma concentration is not clear and the dose should therefore be titrated based on clinical response.	C_{ss} sertraline versus EM: PM: about 150%

[a]: corrected for dose

Risk group	-

Comments:

- <u>Possible relationship between CYP2C19 polymorphisms and depression</u>
  - 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). Howe-

ver, 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 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 sertraline oral clearance is decreased in PM patients (Rudberg 2008 and Wang 2001), but only slightly increased in UM patients (Rudberg 2008). Adverse events have been observed more frequently among PM patients (Grasmader 2004). CPIC recommends a 50% dose reduction or consideration of an alternative SSRI that is not predominantly metabolised by CYP2C19 in PM patients. The percentage dose reduction is derived from percentage differences in oral clearance calculated/estimated by Stingl JC et al. Mol Psychiatry 2013;18:273-87. This review calculates the dose adjustment on the basis of sertraline kinetic parameters instead of sertraline+desmethylsertraline kinetic parameters. This therefore includes the Wang 2001 data (single dose, PM versus EM+IM+UM) in the calculation alongside to the Rudberg 2008 data. CPIC does not recommend dose adjustments for UM patients, but consideration of an alternative SSRI that is not primarily metabolised by CYP2C19 if UM patients do not respond to an adequate sertraline maintenance dose. CPIC classifies the strength of both recommendations as optional given that there is only limited evidence. No action is needed for IM patients. CPIC classifies the recommendation to initiate the standard initial dose in IM patients as strong.

  The recommendations are as follows:

  - *1/*17 and UM: no action needed at the start of the treatment. If patients do not respond to the recommended maintenance dose: 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 9-4-2018, there was not a more recent version of the recommendations present on the PharmGKB- and on the CPIC-site.

Date of literature search: 4 April 2018.

	Phenotype	Code	Gene-drug interaction	Action	Date
Dutch Pharmaco-genetics Working Group Decision	PM	4 C	Yes	Yes	14 May 2018
	IM	4 A	Yes	No	
	UM	4 AA	Yes	No	

Mechanism:

Sertraline is mainly converted by CYP2C19 to the active metabolite desmethylsertraline. Results of the only study that measured steady state concentrations of desmethylsertraline suggest that CYP2C19 also plays an important role in desmethylsertraline metabolism.

Although desmethylsertraline has antidepressant activity, the activity is low and not clinically relevant at the standard sertraline dose. For this reason, most Dutch hospitals use only the sertraline concentration for therapeutic drug monitoring (therapeutic range: 50-300 µg/L) (http://tdm-monografie.org/monografie/ssri-selectieve-serotonine-heropnameremmers). However, some hospitals use the sum of the sertraline and desmethylsertraline concentrations for therapeutic drug monitoring (therapeutic range: 50-250 µg/L).

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