CYP2C19: escitalopram 1820 to 1822

↓ = decrease, 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 homozygous EM or homEM in references, *1/*17) (normal CYP2C19 enzyme activity), IM = intermediate metaboliser (*1/*2, *1/*3, also 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, QTcF-interval = QT-interval corrected for heart rate with Fridericia's formula, S = significant, SmPC = summary of product characteristics, SSRI = selective serotonin reuptake inhibitor, $t_{1/2}$ = half-life, 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 escitalopram to a metabolite with limited antidepressant activity. The escitalopram dose required for therapeutic or supratherapeutic plasma concentrations is therefore lower for patients with reduced CYP-2C19 activity (IM and PM) and higher for patients with increased CYP2C19 activity (UM). Studies have shown a distinct effect on escitalopram plasma concentrations in IM, PM and UM patients. However, escitalopram has a broad therapeutic range.

UM: Seven studies (Jukić 2018; Hodgson 2015; Hodgson 2014;=Huezo-Diaz 2012; Brasch-Andersen 2011; Ohlsson Rosenborg 2008 and Rudberg 2008) provide data for a total of 139 UMs. One study investigated UM in combination with *1/*17 (approximately 9 UM patients) (Bishop 2015). Six of these studies did not find a significant effect on therapeutic efficacy (Bishop 2015 (indication autism spectrum disorder); Hodgson 2014 (indication depression); Brasch-Andersen 2011 (indication neuropathic pain); total of 39 UM patients) or side effects (Hodgson 2015; Ohlsson Rosenborg 2008; total of 27 UM patients). In one of the studies that investigated efficacy (Hodgson 2014; 28 UM patients), the maximum dose was 30 mg/day, i.e. higher than the currently permitted maximum dose of 20 mg/day. This study and the study by Bishop in 2015 did not find any genotype effect on dose. This makes it unlikely that there would have been a difference in efficacy between UM and EM patients at the maximum dose of 20 mg/day. However, the seventh and by far largest study (Jukić 2018; 97 UM), showed an increase in the percentage of patients who switched to another antidepressant within one year after the last escitalopram plasma concentration measurement. Together with a higher percentage of patients with a subtherapeutic escitalopram plasma concentration at a dose of 10 mg/day, this suggested a decreased efficacy of escitalopram treatment in these patients. For this reason, the working group decides to recommend therapy adjustment for UM receiving escitalopram (yes/yes-interaction).

IM and PM: Four studies out of five studies, including a total of 166 IM and PM patients (around 29 PM patients), did not find an increase in side effects in IM and/or PM patients (Ng 2013, Kumar 2014, Hodgson 2015 and Asakura 2016), despite the fact that the maximum dose in three of the four studies was higher than 20 mg/day (30 mg/day in Ng 2013 and Hodgson 2015) and Kumar 2014 and Hodgson 2015 did not find a difference in dose between the genotype groups. However, the fifth and by far largest study (Jukić 2018; 588 IM and 88 PM), showed an increase in the percentage of PM who switched to another antidepressant within one year after the last escitalopram plasma concentration measurement. Together with the percentage of patients with a subtherapeutic escitalopram plasma concentration at a dose of 10 mg/day being reduced to zero, this suggested an increase in escitalopram adverse drug reactions in these patients.

As escitalopram can cause QT prolongation and torsades de pointes, the maximum dose for patients aged < 65 years is 20 mg and for patients aged ≥ 65 years 10 mg, both once daily. These doses would lead to higher plasma concentrations of escitalopram and therefore an increased risk of QT prolongation in IM and PM patients. However, Kumar 2014 did not find any difference in QT_c-interval between IM+PM patients and EM patients, although this was a small study including only 21 IM and 1 PM. In addition, Asakura 2016 did not find an increase in QTcF-interval for 21 PM compared to EM+IM. However, because both studies are small and torsades de pointes is a rare adverse drug reaction, these studies

do not provide solid evidence for a lack of effect on the QT_c-interval and risk of torsades de pointes. Moreover, in Kumar 2014, the groups were not comparable, because the percentage of women was significantly lower among IM+PM patients than among EM patients. Women had a 3.7% longer QT_c-interval than men. Also, the percentage of patients using a CYP2C19 substrate, inhibitor or inducer was significantly higher in the IM+PM patient population than in the EM patient population. There was a trend for a 2.8% longer QT_c-interval among patients using this co-medication.
Six out of seven studies (with a total of 191 IM+PM, including approximately 46 PM) found no difference in response for IM and/or PM (Tsai 2010, Brasch-Andersen 2011, Ng 2013, Hodgson 2015, Bishop 2015 and Asakura 2016). He 2018 (36 IM and 8 PM) found an effect on response, but this mainly concerned the timing of response. Response occurred earlier for PM versus IM versus EM.
As IM and PM lead to a distinct increase in escitalopram plasma concentration and an article not included in this risk analysis shows distinct dose and therefore plasma concentration dependent QT prolongation (Castro 2013), a decision was made to include a warning (yes/yes-interactions). The recommendation is to lower the maximum dose in IM and PM patients to such an extent, that the escitalopram 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 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 therapeutic recommendation
Dose adjustments have been calculated on the basis of escitalopram AUC or C_{ss}.
Where the effect is only known versus EM + UM (e.g. in Waade 2014), the effect of EM + UM is assumed to be similar to that of EM, due to the much lower prevalence of UM.

UM: Based on the comparison of exposure data between UM and EM (including a total of 120 UM), the weighted mean of the calculated dose adjustment would be a dose increase to 128% of the normal dose (median 149%; range 118-188%). The relatively large difference between the weighted mean and median values indicates a high uncertainty in the calculated dose increase. In addition, increasing the dose to such extent that the plasma concentration in UM becomes higher than in EM is unwanted, because of the potential of escitalopram to cause QT prolongation. For this reason, the working group decides to recommend an alternative antidepressant instead of a dose increase of escitalopram.

PM: The weighted mean of the calculated dose adjustment for PM is a dose reduction to 39% (18-60%, median 54%). Considering the median value and the calculated dose adjustment of 50% stated in the SmPC, this is translated to a workable percentage of 50%, i.e. a maximum dose for patients < 65 years of 10 mg and of 5 mg for patients ≥ 65 years.

IM: The weighted mean of the calculated dose adjustment for IM is a dose reduction to 68% (49-83%, median 61%). This is translated to a workable percentage of 75%, i.e. a maximum dose for patients < 65 years of 15 mg and of 7.5 mg for patients ≥ 65 years.

Recommendation concerning pre-emptive genotyping, including justification of choices:
The Dutch Pharmacogenetics Working Group considers genotyping before starting escitalopram 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 escitalopram 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 escitalopram indicates that the escitalopram plasma concentration in CYP2C19 PM is twice the plasma concentration in CYP2C19 EM, but neither mentions CYP2C19 PM as a contra-indication for escitalopram 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
Tsuchimine S et al. Effects of cytochrome P450 (CYP) 2C19 genotypes on steady-state plasma concentrations of escitalopram and its desmethyl metabolite in Japanese patients with depression.
Ther Drug Monit 2018 Mar 22 [Epub ahead of print].
PubMed PMID: 29570504.</td>
<td>3

IM: AA
PM: A</td>
<td>412 patients with major depressive disorder were treated with escitalopram once daily for a minimum of 2 weeks. 110 patients received escitalopram 5 mg/day, 113 patients 10 mg/ day, 71 patients 15 mg/day and 118 patients 20 mg/day.
Blood samples were taken 14-16 hours after the last escitalopram dose.
Relevant co-medication was not excluded.

Genotyping:
- 134x EM
- 235x IM
- 43x PM

Results:
<table>
<tr><td colspan="2">Dose-corrected citalopram steady state plasma concentration compared to EM (3.5 ng/ml.mg):</td></tr>
<tr><td>IM</td><td>x 1.20 (NS)</td></tr>
<tr><td>PM</td><td>x 1.74 (S)</td></tr>
<tr><td colspan="2">Analysis of covariance showed an association between the CYP2C19 genotype and the citalopram plasma concentration (S).</td></tr>
</table>

NOTE: Genotyping was for *2 and *3. These are the most important gene variants in this Japanese population.</td>
<td>Authors’ conclusion:
‘These findings suggest that the CYP2C19 variants are associated with steady-state plasma concentrations of escitalopram to some extent but are not associated with desmethylescitalopram.’

Dose-corrected C_{ss} versus EM:
IM: 120%
PM: 174%</td>
</tr>
<tr>
<td>ref. 2
Jukić MM et al. Impact of CYP2C19 genotype on escitalopram exposure and therapeutic failure: a retrospective study based on 2,087 patients.
Am J Psychiatry 2018 Jan 12 [Epub ahead of print].
PubMed PMID: 29325448.</td>
<td>3

PM: C
UM: C</td>
<td>2087 patients were treated with escitalopram. Plasma concentration measurements were performed as part of the clinical follow-up. Blood samples were taken 10-30 (mean 21.7) hours after the last escitalopram dose. Escitalopram plasma concentrations were normalised to a dose of 10 mg/day.
Therapeutic failure was defined as a switch to another antidepressant within 1 year after the last measurement of the escitalopram plasma concentration.
Subtherapeutic escitalopram plasma concentrations were defined as lower than 25 nM. The Association for Neuropsychopharmacology and Pharmacopsychiatry uses 15 ng/ml (46 nM) as a cut-off point.
Relevant co-medication was not excluded.

Genotyping:
- 1344x EM (837x *1/*1, 507x *1/*17)
- 558x IM (437x *1/null, 121x *17/null)
- 88x PM
- 97x UM

Results:
<table>
<tr><td colspan="7">Results compared to *1/*1:</td></tr>
<tr><td></td><td>PM</td><td>*1/ null</td><td>*17/ null</td><td>*1/ *17</td><td>UM</td><td>value for *1/*1</td></tr>
<tr><td>% of patients switched to another antidepressant</td><td>x 2.60 (S) (OR = 3.30)</td><td>x 1.14 (NS)</td><td>x 1.19 (NS)</td><td>x 1.51 (S) (OR = 1.61)</td><td>x 2.45 (S) (OR = 3.03)</td><td>11.8 %</td></tr>
</table></td>
<td>Authors’ conclusion:
‘The CYP2C19 genotype had a substantial impact on exposure and therapeutic failure of escitalopram, as measured by switching of antidepressant therapy. The results support the potential clinical utility of CYP2C19 genotyping for individualization of escitalopram therapy.’</td>
</tr>
</table>

<table>
<tr>
<td>ref. 2, continuation</td>
<td>IM: A</td>
<td>
<table>
<tr><td>dose-normalised C_{ss} escitalopram</td><td>x 3.27 (S)</td><td>x 1.63 (S)</td><td>x 1.39 (S)</td><td>x 0.90 (S)</td><td>x 0.82 (S)</td><td>32.0 nM</td></tr>
<tr><td>% of patients with sub-therapeutic C_{ss} escitalopram (< 25 nM) (at a dose of 10 mg per day)</td><td>x 0.00 (S)</td><td>x 0.24 (S) (OR = 0.20)</td><td>x 0.49 (S) (OR = 0.44)</td><td>x 1.36 (S) (OR = 1.50)</td><td>x 1.49 (S) (OR = 1.70)</td><td>20.1 %</td></tr>
<tr><td>escitalopram dose</td><td>x 0.70</td><td>x 0.88</td><td>x 0.81</td><td>x 1.01</td><td>x 0.95</td><td>18.0 mg/ day</td></tr>
<tr><td colspan="6">NS (significance not determined)</td></tr>
<tr><td colspan="7">The authors indicate that the increased incidence of therapeutic failure for UM and *1/*17 (defined as a switch to another antidepressant within 1 year of the last escitalopram plasma concentration measurement) might be related to the increased severity of depression they previously found in these patients (Jukić 2017, see ‘Comments’ below).</td></tr>
</table>

NOTE: Genotyping was for *2, *3, *4 (null alleles) and *17. These are the most important gene variants in this Norwegian population.
</td>
<td>Dose-normalised C_{ss} versus EM:
IM: 164%
PM: 339%
UM: 85%</td>
</tr>
<tr>
<td>ref. 3
He Q et al. Correlation between cytochrome P450 2C19 genetic polymorphism and treatment response to escitalopram in panic disorder. Pharmacogenet Genomics 2017;27:279-284. PubMed PMID: 28614176.</td>
<td>4</td>
<td>78 patients with panic disorder were treated with escitalopram 10 mg/day for 8 weeks. Patients with both a minimal score of 10 on the Chinese version of Panic Disorder Severity Scale (PDSS-CV) and a minimal score of 14 on the Hamilton Anxiety Scale (HAMA-14) were included. Patients were excluded if they had evidence of severe physical diseases such as cardiovascular disease, if they had any comorbid psychiatric or substance use disorders, if they had received treatment with antidepressants such as SSRIs or serotonin-norepinephrine reuptake inhibitors in the past 4 weeks or if they received any psychological therapy in the study period.
PDSS-CV has 7 items rated on a 0-4 point scale.
HAMA-14 has 14 items rated on a 0-4 point scale.
Relevant co-medication was excluded. Only short-acting sleeping pills (zopiclone or zolpidem) were used concomitantly for no more than 2 weeks.
Of the original group of 90 patients, 6 could not complete the assessments (e.g. because of restlessness and anxiety), one dropped out because of side effects and five were unwilling to continue.

Genotyping:
- 34x EM
- 36x IM
- 8x PM

Results:
<table>
<tr><td colspan="5">PM versus IM versus EM:</td></tr>
<tr><td></td><td>treat-</td><td>PM</td><td>IM</td><td>value</td></tr>
</table>
</td>
<td>Authors’ conclusion:
‘The CYP2C19 genetic polymorphism is associated with escitalopram treatment response in Chinese patients with panic disorder. CYP2C19 PM could play a key role in early treatment response of escitalopram.’</td>
</tr>
</table>

<table>
<tr><td>ref. 3, continuation</td><td>PM: AA[#]
IM: AA[#]</td><td>
<table>
<tr><td></td><td>ment period</td><td></td><td></td><td>for EM</td></tr>
<tr><td rowspan="2">% of patients with PDSS-CV response</td><td rowspan="2">2 weeks</td><td>x 2.66</td><td>x 2.13</td><td rowspan="2">23.5%</td></tr>
<tr><td colspan="2">S for PM versus IM versus EM</td></tr>
<tr><td rowspan="2"></td><td rowspan="2">4 weeks</td><td>x 1.79</td><td>x 1.29</td><td rowspan="2">55.9%</td></tr>
<tr><td colspan="2">S for PM versus IM versus EM</td></tr>
<tr><td rowspan="2"></td><td rowspan="2">8 weeks</td><td>x 1.26</td><td>x 1.08</td><td rowspan="2">79.4%</td></tr>
<tr><td colspan="2">NS for PM versus IM versus EM</td></tr>
<tr><td rowspan="2">% of patients with HAMA-14 response</td><td rowspan="2">2 weeks</td><td>x 4.25</td><td>x 2.05</td><td rowspan="2">17.6%</td></tr>
<tr><td colspan="2">S for PM versus IM versus EM</td></tr>
<tr><td rowspan="2"></td><td rowspan="2">4 weeks</td><td>x 1.89</td><td>x 1.26</td><td rowspan="2">52.9%</td></tr>
<tr><td colspan="2">S for PM versus IM versus EM</td></tr>
<tr><td rowspan="2"></td><td rowspan="2">8 weeks</td><td>x 1.31</td><td>x 1.05</td><td rowspan="2">76.5%</td></tr>
<tr><td colspan="2">NS for PM versus IM versus EM</td></tr>
<tr><td rowspan="2">reduction in PDSS-CV score</td><td rowspan="2">2 weeks</td><td>x 1.31</td><td>x 1.14</td><td rowspan="2">32.45</td></tr>
<tr><td colspan="2">NS for PM versus IM versus EM</td></tr>
<tr><td rowspan="2"></td><td rowspan="2">4 weeks</td><td>x 1.39</td><td>x 1.01</td><td rowspan="2">49.66</td></tr>
<tr><td colspan="2">S for PM versus IM versus EM</td></tr>
<tr><td rowspan="2"></td><td rowspan="2">8 weeks</td><td>x 1.34</td><td>x 1.04</td><td rowspan="2">63.12</td></tr>
<tr><td colspan="2">S for PM versus IM versus EM</td></tr>
<tr><td rowspan="2">reduction in HAMA-14 score</td><td rowspan="2">2 weeks</td><td>x 1.42</td><td>x 1.15</td><td rowspan="2">34.39</td></tr>
<tr><td colspan="2">NS for PM versus IM versus EM</td></tr>
<tr><td rowspan="2"></td><td rowspan="2">4 weeks</td><td>x 1.36</td><td>x 1.02</td><td rowspan="2">51.51</td></tr>
<tr><td colspan="2">S for PM versus IM versus EM</td></tr>
<tr><td rowspan="2"></td><td rowspan="2">8 weeks</td><td>x 1.30</td><td>x 1.07</td><td rowspan="2">62.79</td></tr>
<tr><td colspan="2">S for PM versus IM versus EM</td></tr>
</table>

NOTE: Genotyping was for *2, *3 and *17. *17 was not found in this Chinese population.</td><td></td></tr>
<tr><td>ref. 4
Asakura S et al. Long-term administration of escitalopram in patients with social anxiety disorder in Japan. Neuropsychiatr Dis Treat 2016;12:1817-25. PubMed PMID: 27524899.</td><td>3</td><td>158 patients with social anxiety disorder were treated with escitalopram for 52 weeks. The escitalopram dose was 10 mg/day during the first week and was increased to 20 mg/day for the majority of patients (68.4%, with 56.3% of total patients remaining on 20 mg/day). 128 patients (81.0%) completed the study. Of the 30 patients who did not, 17 withdrew because of adverse events. Included patients had a total score ≥ 60 on the Liebowitz Social Anxiety Scale -Japanese Version (LSAS-J) and ≥ 4 on the Clinical Global Impression - Severity Scale and exhibited fear/anxiety or avoidance traits in at least four items of the LSAS-J, of which ≥ 2 were social interaction items at screening and baseline visits. Patients with a total score ≥ 15 on the Montgomery Åsberg Depression Rating Scale were excluded. Adverse events were reported by 82.9% of patients. Most were transient and occurred during the first week (median time of 5.5 days and median duration of 11 days). Adverse drug reactions (adverse events where a causal relationship to escitalopram could not be ruled</td><td>Authors’ conclusion: ‘The incidence of adverse drug reactions was similar in extensive and poor metabolizers of cytochrome P450 2C19.’</td></tr>
</table>

<table>
<tr>
<td>ref. 4, continuation</td>
<td>PM: AA</td>
<td>out) were reported by 57.6% of patients. Most adverse drug reactions occurred during the first 12 weeks and all were mild or moderate. The most common adverse drug reactions were somnolence and nausea. Two patients reported serious adverse events (deep vein thrombosis and anal fissure), neither of which was considered treatment-related. There were no clinically significant changes in the mean values of ECG parameters. No patients had a QTcF interval > 500 ms during treatment. One patient had a change > 60 ms (68 ms at week 52 and a QTcF of 469 ms).
The LSAS-J has two subscales, fear/anxiety and avoidance, each consisting of 24 items. Response was defined as ≥ 30% improvement in LSAS-J total score. Remission was defined as a LSAS-J total score ≤ 30. Relevant co-medication was not excluded.

Genotyping:
- 137x EM+IM
- 21x PM

Results:
<table>
<tr><td colspan="3">Results compared to EM+IM:</td></tr>
<tr><td></td><td>PM</td><td>value for EM+IM</td></tr>
<tr><td>% of patients with adverse drug reactions</td><td>x 0.90 (NS)</td><td>58.4%</td></tr>
<tr><td>change in QTcF interval from baseline to end of treatment</td><td>x 0.70 (NS)</td><td>5.7 ms</td></tr>
<tr><td>% of patients completing the study</td><td>x 0.87 (NS)</td><td>82.5%</td></tr>
<tr><td>% of responders</td><td>x 0.96 (NS)</td><td>69.4%</td></tr>
<tr><td>% of patients with remission at week 52</td><td>x 0.72 (NS)</td><td>27.9%</td></tr>
<tr><td>decrease in the LSAS-J total score</td><td>x 0.94 (NS)</td><td>45.1</td></tr>
<tr><td colspan="3">The significance of the differences between PM and EM+IM was not determined.</td></tr>
</table>
NOTE: The gene variants genotyped were not specified and PM and EM were not defined explicitly.</td>
<td></td>
</tr>
<tr>
<td>ref. 5
Bishop JR et al. Escitalopram pharmacogenetics: CYP2C19 relationships with dosing and clinical outcomes in autism spectrum disorder. Pharmacogenet Genomics 2015:548-54. PubMed PMID: 26313485.</td>
<td>3</td>
<td>89 patients between 4 and 45 years with autism spectrum disorder were treated with escitalopram for 6 weeks (initial dose 2.5 mg/day; then weekly increases to 20 mg/day or until side effects occurred). Other psychoactive medication and other serious medical disorders were excluded, but co-medication influencing CYP2C19 was not.

Genotyping:
- 40x EM (*1/*1)
- 23x IM+PM (22x IM + 1x PM)
- 26x *1/*17+UM (~ 17x *1/*17 and 9x UM)

Results:
<table>
<tr><td>IM+PM versus *1/*1 versus *1/*17+UM:</td></tr>
<tr><td>No difference in:
- Improvement and rate of improvement of symptoms (irritability, hyperactivity, inappropriate speech, lethargy, stereotypy and all</td></tr>
</table></td>
<td>Authors’ conclusion: ‘Clinical symptoms as measured by the ABC-CV rating scale improved over the course of treatment and the magnitude or the rate of improvement did not differ significantly across genotype groups. In an examination of tolerance to the titration schedule used in the study, secondary analyses identified that ultra-rapid metabolizers had a slower rate of dosing change compared with other groups.’</td>
</tr>
</table>

<table>
<tr>
<td>ref. 5, continuation</td>
<td>IM+PM: AA

*1/*17+ UM: A</td>
<td>
symptoms) (NS)
- The final daily dose (NS)

Rate of dose increase versus *1/*1 for different periods (↓ = decrease):
<table>
<tr><td></td><td>Overall period</td><td>Week 4</td><td>Week 5</td><td>Week 6</td></tr>
<tr><td></td><td></td><td colspan="3">versus week 1</td></tr>
<tr><td>IM+PM</td><td>NS</td><td></td><td></td><td></td></tr>
<tr><td>*1/*17+ UM</td><td>trend for ↓ (p = 0.09)</td><td>↓ (S)</td><td>↓ (S)</td><td>↓ (S)</td></tr>
</table>
NOTE: Alleles *2, *3 and *17 were genotyped
</td>
<td></td>
</tr>
<tr>
<td>ref. 6
Hodgson K et al. Exploring the role of drug-metabolising enzymes in antidepressant side effects. Psychopharmacology (Berl) 2015;232: 2609-17.
PubMed PMID: 25761838.</td>
<td>4

PM: AA
IM: AA
UM: AA</td>
<td>
The same 340 patients who participated in the Hodgson 2014 and Huezo-Diaz 2012 studies were monitored weekly for 12 weeks for the presence or absence of 21 side effects using a self-report checklist. CYP2C19-inhibiting co-medication was not excluded and doses were variable, but corrections were made for both.

Genotyping (calculated on the basis of stated percentages):
- 130x EM (*1/*1)
- 88x *1/*17
- 27x *17/*2
- 67x *1/*2
- 6x PM
- 22x UM

Results:
PM versus *1/*2 versus *17/*2 versus *1/*1 versus *1/*17 versus UM:
No difference in:
- The number of side effects per patient (NS for the trend and for PM versus (not PM))
- The occurrence of each of the 21 measured side effects (21 times NS)
- The percentage of patients who withdrew from the study (NS)

NOTE 1: The escitalopram plasma concentration was not associated with the number of side effects per patient or the occurrence of 18 of the 21 measured side effects (19 times NS). The occurrence of the side effect dry mouth increased with escitalopram plasma concentration (OR = 1.48) and to a similar extent with desmethylescitalopram and the sum of both concentrations (3 times S). Diarrhoea occurred less frequently with higher desmethylescitalopram/escitalopram ratios (OR = 0.60; S). Occurrence of vertigo increased with desmethylescitalopram plasma concentration (OR = 1.56; S).

NOTE 2: Alleles *2, *3 and *17 were genotyped. There were no *3 patients in this group.
</td>
<td>Authors' conclusion: 'In this sample where escitalopram dosage is titrated using clinical judgement, CYP2C19 genotypes do not explain differences between patients in side effects.'</td>
</tr>
<tr>
<td>ref. 7
Kumar Y et al. CYP2C19 variation, not citalopram dose nor serum level, is</td>
<td>3</td>
<td>80 patients were treated with escitalopram 10-60 mg/day. Relevant co-medication was not excluded and the percentage of patients with relevant co-medication was higher among IM+PM patients than among EM patients (68% versus 36%) (S). The percentage of</td>
<td>Authors' conclusion: 'In the 80 patient escitalopram cohort, there was no significant difference in QTc between</td>
</tr>
</table>

<table>
<tr>
<td>associated with QTc prolongation.
J Psychopharmacol 2014;28:1143-8.
PMID: 25122046.

ref. 7, continuation</td>
<td>IM+PM:
AA</td>
<td>women was lower among IM+PM patients than among EM patients (50% versus 76%) (S).

Genotyping:
- 58x EM
- 22x IM+PM (21x IM + 1x PM)

Results:
<table>
<tr><td colspan="2">QT_c-interval versus EM (432.8 ms):</td></tr>
<tr><td>IM+PM</td><td>NS</td></tr>
<tr><td colspan="2">The groups were also not comparable, because the percentage of women was lower among IM+PM patients. Women had a 3.7% longer QT_c-interval than men (438.6 versus 423.0 ms) (S).
The percentage of patients with relevant co-medication was higher among IM+PM patients. There was a trend for a 2.8% longer QT_c-interval among patients using CYP2C19 substrates, inhibitors or inducers (440.2 versus 428.4 ms) (p = 0.058, NS).</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 20 mg/day (NS)</td></tr>
</table>

NOTE: There was no significant association between dose and QT_c-interval (NS).</td>
<td>phenotype groups. ….. Of 75 citalopram patients, the EM group had significantly shorter QTc intervals than a combined IM+PM group. … 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. 8
Waade RB et al. Impact of age on serum concentrations of venlafaxine and escitalopram in different CYP2D6 and CYP2C19 genotype subgroups. Eur J Clin Pharmacol 2014;70:933-40. PubMed PMID: 24858822.</td>
<td>4

IM: AA
PM: AA</td>
<td>541 patients were treated with escitalopram (2.5-120 mg/day). Co-medication influencing CYP2C19 or CYP3A4 was excluded. It was however not known whether the overview of co-medication used was complete.

Genotyping:
- 367x EM
- 145x IM
- 29x PM

Results:
<table>
<tr><td colspan="2">Dose-corrected plasma concentration of escitalopram versus EM (2.8 nmol/L per mg/day):</td></tr>
<tr><td>IM</td><td>x 1.9 (NS, significance not determined)</td></tr>
<tr><td>PM</td><td>x 3.6 (NS, significance not determined)</td></tr>
</table>

<table>
<tr><td colspan="2">Dose-corrected plasma concentration of escitalopram for patients > 65 years versus patients < 40 years:</td></tr>
<tr><td>EM</td><td>x 1.3 (S)</td></tr>
<tr><td>IM</td><td>x 1.4 (S)</td></tr>
<tr><td>PM</td><td>x 1.4 (NS, trend, p = 0.1)</td></tr>
<tr><td colspan="2">The escitalopram/desmethylescitalopram metabolic ratio was not different between the age groups.
Although the dose was not lower for PM patients aged > 65 years, the percentage of patients with plasma concentrations above the therapeutic range (> 250 nmol/L) was not different than that</td></tr>
</table>
</td>
<td>Authors’ conclusion: ‘A genotype-related effect of age was not observed for escitalopram (<1.5-fold age differences in all CYP2C19 subgroups).’

Dose-corrected C_{ss} versus EM:
IM: 187%
PM: 359%</td>
</tr>
</table>

<table>
<tr><td>ref. 8, continuation</td><td></td><td>among patients < 40 years (NS).
The dose instituted for IM and EM patients was lower among patients aged > 65 years than among those aged < 40 years (both S).

<table><tr><td colspan="2">Escitalopram/desmethylescitalopram metabolic ratio in women versus men:</td></tr><tr><td>EM</td><td>x 0.85 (S)</td></tr><tr><td>IM</td><td>NS</td></tr><tr><td>PM</td><td>x 1.8 (S)</td></tr><tr><td colspan="2">The dose-corrected escitalopram plasma concentration was 1.8-fold higher among PM women than among PM men (S).
Whether the difference between PM and EM was significant was not determined.</td></tr></table>
NOTE: Alleles *2, *3 and *4 were genotyped</td><td></td></tr>
<tr><td>ref. 9
Hodgson K et al. Genetic differences in cytochrome P450 enzymes and antidepressant treatment response. J Psychopharmacol 2014;28:133-41. PubMed PMID: 24257813.</td><td>4

PM: AA
IM: AA
UM: AA</td><td>The severity of depressive symptoms was measured weekly during 12 weeks of treatment using the Montgomery-Åsberg Depression Rating Scale in the same 443 patients who participated in the Huezo-Diaz 2012 study. Co-medication with weak CYP2C19 inhibitors was not excluded, but corrections were made for this. The dose varied, but there was no relationship between CYP2C19 genotype and dose.

Genotyping (calculation based on stated percentages):
- 170x EM (*1/*1)
- 120x *1/*17
- 36x *17/*2
- 80x *1/*2
- 9x PM
- 28x UM

Results:
<table><tr><td>PM versus *1/*2 versus *17/*2 versus *1/*1 versus *1/*17 versus UM:</td></tr><tr><td>No difference in:
- Response (NS)
- Dose (NS)</td></tr><tr><td>The same genotype distribution results were found in fewer than 6 phenotype groups.</td></tr></table>
NOTE 1: When corrections for dose were made, there was no association between escitalopram plasma concentration at 8 weeks and response (n = 235) (NS). When no corrections for dose were made, there was a negative association (n = 266) (S). The latter is probably caused by the fact that the dose was increased for patients not responding adequately to the treatment. There was no association between desmethylescitalopram plasma concentration and response (NS). The response to treatment was better among patients in whom the plasma concentrations were measured than among patients in whom this was not the case (S). The plasma concentrations measured also differed between the participating centres, also after correction for dose (S), while the CYP2C19 genotypes did not differ. The reasons for this were not known.

NOTE 2: genotyping was performed for *2, *3 and *17.</td><td>Authors’ conclusion: ‘While there is a significant relationship between the CYP2C19 genotype and serum concentration of escitalopram, the genotype is not predictive of differences in treatment response. Furthermore, differences in antidepressant serum concentrations are not associated with variability in treatment response.’</td></tr>
</table>

		There were no *3 patients in this group.	
ref. 10 Ng C et al. Pharmacogenetic polymorphisms and response to escitalopram and venlafaxine over 8 weeks in major depression. Hum Psychopharmacol 2013;28:516-22. PubMed PMID: 24014145.	3 IM+PM: AA[#]	62 patients were treated with escitalopram for 8 weeks (10 mg/day for 1 week followed by dose adjustment guided by response and adverse events; the eventual mean dose was 18.6 mg/day (5-30 mg/day)). Other psychoactive co-medication and clinically significant medical disorders were excluded, but co-medication influencing CYP2C19 was not. Response was measured using the 17-item Hamilton Depression Scale, side effects using the UKU scale. Genotyping: - 39x EM+UM - 23x IM+PM Results: IM+PM versus EM+UM: No difference in: - Decrease in depression (NS) - Occurrence of neurological, psychiatric and 'other' side effects at 1 week (NS) UKU score for autonomous side effects, e.g. sweating and gastrointestinal symptoms at 1 week versus EM+UM (score 1.82): IM+PM: x 0.86 (S) The authors stated that it was unlikely that this difference was clinically relevant. NOTE: definitions of EM, IM, PM and UM and the specific alleles were not given.	Authors' conclusion: 'In our study, CYP2C19 PMs/IMs were not associated with increased side effects scores in the escitalopram group. The apparent opposite effect in the autonomic domain for the Caucasian escitalopram group may possibly be related to greater conversion to metabolites but is unlikely to be clinically significant.'
ref. 11 Huezo-Diaz et al. CYP2C19 genotype predicts steady state escitalopram concentration in GENDEP. J Psychopharmacol 2012;26:398-407. PubMed PMID: 21926427.	4 UM: A IM: A	196 depressed patients aged 19-72 years were treated with escitalopram for 8 weeks (initial dose 10 mg/day, if needed increased to 20 mg/day after 2 weeks, if needed increased to 30 mg/day after another 2 weeks). Relevant co-medication and CYP2D6 genotype were included in the analysis as potential confounders. Co-medication did not have a significant effect on the results. Genotyping: - 11x UM - 128x EM (58x *17/*1, 70x *1/*1) - 53x IM (15x *17/null allele, 38x *1/null allele) - 4x PM UM versus EM: - The dose-corrected C_{ss} decreased by 47% (from 1.78 to 0.95 μg/L per mg) (S versus *1/*1, not determined versus *1/*17) - The desmethylescitalopram/escitalopram ratio increased by 67% (from 0.41 to 0.68) (S) IM versus EM: - The dose-corrected C_{ss} increased by 22% (from 1.78 to 2.18 μg/L per mg) (NS) - The desmethylescitalopram/escitalopram ratio decreased by 28% (from 0.41 to 0.30) (S) PM versus EM: - The dose-corrected C_{ss} increased by 67% (from 1.78	Authors' conclusion: 'In conclusion, we have demonstrated an association between CYP2C19 genotype, including the CYP2C19*17 allele, and steady state escitalopram concentration.' C_{ss} escitalopram versus EM: UM: 53% IM: 122% PM: 167%

ref. 11, continuation	PM: A	to 2.97 μg/L per mg) (S) - The desmethylescitalopram/escitalopram ratio decreased by 39% (from 0.41 to 0.25) (NS) The genotype did not influence the N-desmethylescitalopram C_{ss}[a]. The citalopram dose did not differ significantly between the genotypes. NOTE: Alleles *2, *3 and *17 were genotyped.	
ref. 12 Brasch-Andersen C et al. A candidate gene study of serotonergic pathway genes and pain relief during treatment with escitalopram in patients with neuropathic pain shows significant association to serotonin receptor2C (HTR2C). Eur J Clin Pharmacol 2011;67:1131-7. PubMed PMID: 21614492.	3 PM: AA IM: AA UM: AA	34 patients with peripheral neuropathy received escitalopram 20 mg/day for 6 weeks. 11 patients were responders (medium or improved pain relief) and 23 were non-responders (no or limited pain relief). Relevant co-medication was not excluded. Genotyping *2: - 23x EM+UM - 7x IM - 1x PM Genotyping *17: - 19x no *17 - 12x heterozygous for *17 - 2x UM No association was found between polymorphisms and response. This is consistent with the fact that there was also no association between escitalopram plasma concentration and response. NOTE: Alleles *2 and *17 were genotyped.	Authors' conclusion: 'We found no association between CYP2C19 polymorphisms and pain relief, which correlates with the fact that no difference in escitalopram plasmaconcentration between responders and nonresponders was found (data not shown).'
ref. 13 Tsai et al. Genetic polymorphisms of cytochrome P450 enzymes influence metabolism of the antidepressant escitalopram and treatment response. Pharmacogenomics 2010;11:537-46. PubMed PMID: 20350136.	3 PM: A IM: A	100 depressed patients were treated with escitalopram (10 mg/day for 4 weeks, followed by 10-30 mg/day guided by clinical response for 4 weeks). Relevant co-medication was not excluded. CYP2C19*2 was not in Hardy-Weinberg equilibrium. Genotyping: - 47x EM - 37x IM (33x *1/*2, 4x *1/*3) - 16x PM (15x *2/*2, 1x *2/*3) PM versus (EM+IM): - No difference in response as measured by the Hamilton Depression and Anxiety Scales (NS) PM versus EM: - The escitalopram C_{ss} at 4 weeks increased by approximately 100% (S) - The desmethylescitalopram/escitalopram ratio decreased by approximately 67% (S) - No significant difference in escitalopram dose (NS) IM versus EM: - No significant difference in escitalopram C_{SS} at 4 weeks (NS) - The desmethylescitalopram/escitalopram ratio decreased by approximately 33% (S) - No significant difference in escitalopram dose (NS)	Authors' conclusion: 'Our results suggest that the genetic polymorphisms in CYP2C19 may be influencing escitalopram serum concentrations, and that specific CYP2D6 polymorphisms may be predicting patient treatment outcomes based on gene dosage analyses.'

ref. 13, continuation		NOTE: Alleles *2, *3 and *17 were genotyped, but the allele frequency of *17 was too low (0.5%) to include *17 in the analysis.	
ref. 14 Jin Y et al. Effect of age, weight, and CYP2C19 genotype on escitalopram exposure. J Clin Pharmacol 2010;50:62-72. Pubmed PMID: 19841156.	3 IM+PM: A UM: AA	128 patients were treated with escitalopram (5-20 mg/day). Relevant co-medication was not excluded. The authors did not provide raw data, but data predicted using a population pharmacokinetic model. Genotyping: - 77x EM - 43x IM - 3x PM - 5x UM IM+PM versus EM+UM: - Cl_{cr} decreased by 25% (from 29.73 to 22.23 L/hour) (S) UM versus EM: - No significant difference in Cl_{or} NOTE: Alleles *2, *3 and *17 were genotyped.	Authors' conclusion: 'CYP2C19 genotype, age, and weight strongly influenced the CL/F of escitalopram. These variables may affect patient tolerance of this antidepressant and may provide important information in the effort to tailor treatments to patients' individual needs.'
ref. 15 Noehr-Jensen et al. Impact of CYP2C19 phenotypes on escitalopram metabolism and an evaluation of pupillometry as a serotonergic biomarker. Eur J Clin Pharmacol 2009;65:887-94. Pubmed PMID: 19404631.	3 PM(+IM) : A	13 healthy volunteers were given escitalopram 10 mg for 8 days. Relevant co-medication was not excluded. Genotyping: - 8 EM/IM (7x *1/*1, 1x *1/*2) (EM phenotype) - 5 PM/IM (3x *2/*2, 1x *2/*4, 1x *1/*2) (PM phenotype) PM/IM versus EM/IM: - The $AUC_{0\text{-}24h}$ increased by 86% (from 1501 to 2785 nmol.hour/L) (S) - The $t_{1/2}$ increased by 25% (from 28 to 35 hours) (S) - Cl_{or} decreased by 46% (from 20.6 to 11.1 L/hour) (S) The AUC_{∞} determined on the first day, i.e. after the first dose, was 103% higher in PM/IM patients than in EM/IM patients. Statistical analysis showed that there were similar AUC ratios for PM/IM and EM/IM after single and repeated doses (1.82 and 1.80 respectively). The pupillary reflex measurements did not show clear relationships. The authors concluded that pupillometry cannot be recommended as a serotonergic biomarker. NOTE: Alleles *2 to *4 were genotyped	Authors' conclusion: 'The CYP2C19 polymorphism affects escitalopram metabolism, but the difference does not justify dose adjustment.' $AUC_{0\text{-}24}$ versus EM+IM: PM(+IM): 186%
ref. 16 Ohlsson Rosenborg S et al. Kinetics of omeprazole and escitalopram in relation to the CYP2C19*17 allele in healthy subjects. Eur J Clin Pharmacol 2008;4:1175-79.	4 UM: AA	16 healthy volunteers, 11x *1/*1, 5x *17/*17, received escitalopram 5 mg twice daily for 6 days, no relevant co-medication; *17/*17 versus *1/*1: - The mean $AUC_{0\text{-}12}$ for escitalopram decreased by 21% (NS). - The intra-individual variation in AUC decreased (variation coefficient decreased from 41 to 19). - Non-significant decrease in frequency of side effects (NS). The authors stated that a 21% decrease in AUC cannot be considered clinically significant and that this is no reason for dose adjustment.	Authors' conclusion: 'Concluding from this and previous studies, the CYP2C19*17/*17 genotype may be associated with higher than average clearance of CYP2C19 substrates, but the clinical importance seems limited.' Escitalopram $AUC_{0\text{-}12}$ versus EM: UM: 79%

ref. 17 Rudberg I et al. Impact of the ultrarapid CYP2C19*17 allele on serum concentration of escitalopram in psychiatric patients. Clin Pharmacol Ther 2008;83:322-7.	4 UM: A PM: A IM: A	Retrospective study using therapeutic drug monitoring samples from 166 patients (60x *1/*1, 43x *1/*17, 7x *17/*17, 6x *2/*17 or *3/*17, 34x *1/null allele, 6x PM) treated with escitalopram. Relevant co-medication was excluded. *17/*17 versus *1/*1: - Conc[a] decreased from 2.72 to 1.59 nM/mg per day (S by 42%). *1/*17 versus *1/*1 and *2/*17 + *3/*17 versus *1/*1: - No significant effect. PM versus *1/*1: - Conc[a] increased from 2.72 to 15.5 nM/mg per day (S by 470%). *1/null allele versus *1/*1: - Conc[a] increased from 2.72 to 5.10 nM/mg per day (S by 88%).	Authors' conclusion: 'Although the impact of CYP2C19*17 on serum concentration of escitalopram was less pronounced than defective CYP2C19 alleles, CYP2C19*17 might be associated with increased risk of therapeutic failure of escitalopram treatment.' Escitalopram conc[a] versus EM: UM: 58% PM: 570% IM: 188%
ref. 18 Rudberg I et al. Heterozygous mutation in CYP2C19 significantly increases the concentrations/dose ratio of racemic citalopram and escitalopram (S-citalopram). Ther Drug Monitor 2006;28:102-5.	4 IM: A	43 patients, 27x EM and 16x IM (*1/*2), treated with escitalopram (EM 20 mg/day, IM 22 mg/day), no CYP2C19 inhibitors or inducers as co-medication; IM versus EM: - Sign. increase in conc[a] from 2.6 to 5.3 (S by 104%). - Sign. increase in MR[a] by 100%.	Authors' conclusion: 'Escitalopram 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, 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 204% versus EM.
ref. 19 SPC Lexapro (escitalopram) 05-09-13.	 PM: A	<u>Dose</u>: For patients who are known to be poor metabolisers with respect to CYP2C19, an initial dose of 5 mg daily during the first two weeks of treatment is recommended. Depending on individual patient response, the dose may be increased to 10 mg daily. <u>Pharmacokinetic properties:</u> It has been observed that poor metabolisers with respect to CYP2C19 have twice as high a plasma concentration of escitalopram as extensive metabolisers.	 Maximum dose versus EM: PM: 50%
ref. 20 SmPC Lexapro (escitalopram), USA, 04-01-17.	 PM: A	<u>Adverse events</u>: QTcF interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg) controlled cross-over, escalating multiple-dose study in 113 healthy subjects. The maximum mean (95% upper confidence bound) difference from placebo arm were 4.5 (6.4) and 10.7 (12.7) msec for 10 mg and supratherapeutic 30 mg escitalopram given once daily, respectively. The exposure under supratherapeutic 30 mg dose is similar to the steady state concentrations expected in CYP2C19 poor metabolizers following a therapeutic dose of 20 mg.	 Dose versus EM: PM: 67%

[a] Corrected for dose.

Risk group	IM with CYP2D6 inhibitor

Comments:

- Kinetic data generated after 2012 have only been included if the outcome was analysed by genotype group. Studies only demonstrating an association contribute insufficiently to the data already included. Kinetic studies have only been included if the outcome measures were determined separately for citalopram and escitalopram.
- Escitalopram is the S-enantiomer of citalopram, which is predominantly responsible for the antidepressant and anxiolytic activity.
  The Rudberg, 2006 reference shows 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.
- <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). 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 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 escitalopram and citalopram than *1/*1 patients (Huezo-Diaz 2012, Hodgson 2014, Rudberg 2008). This leads to a higher risk of failure of therapy. There is 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. Bishop 2015 (indication autism spectrum disorder) and Brasch-Andersen 2011 (indication neuropathic pain) have not been used to support the recommendation. Neither found a genotype effect on efficacy. 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 side effects (Noehr-Jensen 2009, Rudberg 2008, Chen 2013 and Fudio 2010). In order to prevent potential side effects, alternative SSRIs not predominantly metabolised by CYP2C19 should be considered. If escitalopram or citalopram are preferred, 50% reduction of the initial dose 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 31-3-2018, 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
Dutch Pharmaco-genetics Working Group decision	IM	4 A	Yes	Yes	14 May 2018
	PM	4 C	Yes	Yes	
	UM	4 C	Yes	Yes	

Mechanism:
Escitalopram is primarily metabolised by CYP2C19 and to a lesser extent by CYP3A4 to N-desmethylescitalopram. Although desmethylescitalopram has antidepressant activity, the activity is low and not clinically relevant at the standard escitalopram dose. N-desmethylescitalopram is converted by CYP2D6 to didesmethylescitalopram.
The upper limit of the therapeutic range of escitalopram is 250 ng/mL. At occupancy rates of the serotonine transporter of less than 80%, escitalopram efficacy is suboptimal.

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	0-2 +

	available, the DPWG recommends adhering to the gene-drug guideline	
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