CYP2D6: fluvoxamine 5993/5994/5995

AUC = area under the time-concentration curve, 95% CI = 95% confidence interval, Cl_{or} = oral clearance, C_{ss} = steady-state plasma concentration, EM = extensive metaboliser (gene dose 1.5-2.5) (normal CYP2D6 enzyme activity), HR = hazard ratio, IM = intermediate metaboliser (gene dose 0,5-1) (decreased CYP2D6 enzyme activity), MR = metabolic ratio, NS = non-significant, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), S = significant, S_t = significant for the trend between the genotype groups, $t_{1/2}$ = half-life, UM = ultra-rapid metaboliser (gene dose $\geq$ 3) (enhanced CYP2D6 enzyme activity).

Disclaimer: The Pharmacogenetics Working Group of the KNMP formulates the optimal recommendations for each phenotype group based on the available evidence. If this optimal recommendation cannot be followed due to practical restrictions, e.g. therapeutic drug monitoring or a lower dose is not available, the health care professional should consider the next best option.

Brief summary and justification of choices:
Fluvoxamine is predominantly metabolised into inactive metabolites by CYP2D6 and CYP1A2. Fluvoxamine shows saturation kinetics, particularly at doses above 100 mg/day or plasma concentrations above 150 ng/mL. The low capacity of CYP2D6 probably contributes to the saturation kinetics and the resulting non-linear dose-concentration relationship of fluvoxamine. Studies found an effect of the CYP2D6 activity on the fluvoxamine AUC or plasma concentration. However, this effect was not very strong and seemed to diminish with increasing doses. For PM, AUCs or plasma concentrations of 131-391% of those in EM or *1/*1 have been observed, for IM of 99-310% of those in EM or *1/*1. Fluvoxamine has a broad therapeutic range.
Two studies evaluated clinical effects in patients. One of these studies (10 IM, initial dose 50 mg/day) found no difference in therapeutic response or the incidence of side effects between the genotypes. The second study (22 IM, initial dose 25 mg/day) found an increased risk of developing a gastrointestinal side effect in the first 6 weeks of treatment for IM in comparison with EM. However, this increase was not due to overdosing. The initial concentration (27.4 ng/mL in IM) was lower than the proposed therapeutic threshold of 61.4 ng/mL. In addition, there was no difference in the incidence of discontinuation of therapy, so no indication of an increased risk of failure of therapy. Finally, a lower initial dose for IM or PM is practically not feasible, since the tablet with the lowest dose contains 50 mg fluvoxamine. So, for these gene-drug interactions, therapy adjustment is not possible and most probably also not useful (yes/no-interactions).
There are no data for UM, the genotype leading to an enhanced CYP2D6 enzyme activity. However, one study found no difference in therapeutic response between the genotypes. In addition, the maximum dose of fluvoxamine is 1.5 times the maximum dose employed in the studies. So, in case UM need higher doses of fluvoxamine a dose increase to this maximum fluvoxamine dose would likely suffice. For this reason, also for UM there is no deviation of the normal practice of response guided dosing needed (yes/no interaction).
You can find an overview of the clinical and kinetic effects per phenotype in the background information text of the corresponding phenotype-drug interaction on the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

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 might differ from the definitions used by the authors of the article.

Source	Code	Effect	Comments
ref. 1 Suzuki Y et al. CYP2D6 genotype and smoking influence fluvoxamine steady-state concentration in Japanese psychiatric patients: lessons for genotype-phenotype association study design in	3	87 patients were treated with fluvoxamine 50-200 mg/day (initial 50 mg/day, then gradual increase to maximum 200 mg/day). Plasma concentrations were determined after a fixed-dose interval of at least 2 weeks. Relevant co-medication was excluded. Smoking was not excluded. 50 patients were non-smokers, 22 smoked 20 or more cigarettes/day and 15 smoked 1-19 cigarettes/day. Genotyping: - 27x gene dose 2 (*1/*1)	Author's conclusion: "While CYP2D6 genotype significantly influenced fluvoxamine concentration in all four dose groups, the percentage variance explained by CYP2D6 decreased as the dose of fluvoxamine increased.

<table>
<tr>
<td>translational pharmacogenetics.
J Psychopharmacol 2011;25:908-14.
PubMed PMID: 20547595.

ref. 1, continuation</td>
<td>IM: A</td>
<td>- 40x gene dose 1-1.5 (34x *1/*10, 6x *1/*5)
- 20x gene dose 0.5-1 (18x *10/*10, 2x *5/*10)

Results:
<table>
<tr><td colspan="5">Median plasma concentration (C_{ss}) at different dosages in comparison with gene dose 2:</td></tr>
<tr><td rowspan="2">dose (mg/ day)</td><td colspan="2">gene dose</td><td rowspan="2">C_{ss} for gene dose 2 (ng/ml)</td><td rowspan="2">% variance explained by CYP2D6 genotype</td></tr>
<tr><td>0.5-1</td><td>1-1.5</td></tr>
<tr><td>50</td><td>x2.1 (S)</td><td>x1.5 (S_t)</td><td>8.2</td><td>12.3</td></tr>
<tr><td>100</td><td>x3.1 (S)</td><td>x2.0 (S_t)</td><td>16.0</td><td>12.0</td></tr>
<tr><td>150</td><td>x2.7 (S)</td><td>x1.7 (S_t)</td><td>35.8</td><td>6.3</td></tr>
<tr><td>200</td><td>x2.0 (S)</td><td>x1.5 (S_t)</td><td>68.1</td><td>4.1</td></tr>
<tr><td colspan="5">There was no significant difference in smoking status between the genotype groups. However, stepwise multiple regression analysis to evaluate the joint effects of smoking status and CYP2D6 genotype on fluvoxamine concentration, resulted in loss of significance of the association with genotype for the doses 150 and 200 mg/day. Despite this, an association with smoking status was not found for these doses.</td></tr>
<tr><td colspan="5">The authors mention a threshold therapeutic fluvoxamine concentration of 61.4 ng/mL. The median plasma concentration is higher than this threshold at a dosage of 200 mg/day for gene dose 2 and a dosage of 150 or 200 mg/day for gene dose 0.5-1.</td></tr>
</table>
NB: Alleles *5 and *10 were genotyped. These are the most prevalent variant alleles in this Asian population.</td>
<td>Smoking status (non-smokers vs. smoking 20 or more cigarettes/d) significantly affected fluvoxamine concentration in the 50 mg/d group only.”

C_{ss} in comparison with *1/*1:
IM: 200-310%</td>
</tr>
<tr>
<td>ref. 2
Sugahara H et al. Effect of smoking and CYP2D6 polymorphisms on the extent of fluvoxamine-alprazolam interaction in patients with psychosomatic disease.
Eur J Clin Pharmacol 2009;65:699-704.
PubMed PMID: 19225771.</td>
<td>3

IM: AA</td>
<td>38 patients were treated with fluvoxamine at an average dose of 1.53 mg/kg per day (0.50-4.62 mg/kg per day). This corresponds to an average dose of 83.3 mg/day. Relevant co-medication and smoking were not excluded. 10 patients were non-smokers, 28 were smokers.

Genotyping:
- 7x gene dose 2 (*1/*1)
- 16x gene dose 1-1.5 (ca. 13x *1/*10, 3x *1/*5)
- 15x gene dose 0.5-1 (ca. 11x *10/*10, 4x *5/*10)

Results:
<table>
<tr><td colspan="2">Dose-corrected and body weight-corrected plasma concentration in comparison with gene dose 2 (48.9 ng.kg.day/mL.mg):</td></tr>
<tr><td>gene dose 1-1.5</td><td>x1.13 (NS)</td></tr>
<tr><td>gene dose 0.5-1</td><td>x1.58 (NS)</td></tr>
<tr><td colspan="2">There was a trend for a larger variance of the dose-corrected and body weight-corrected plasma concentration in the groups with gene doses 0.5-1 and 1-1.5 compared to the group with gene dose 2 (p = 0.058).</td></tr>
</table>
NB: Alleles *4, *5, *10 and *14 were genotyped. These are the most prevalent variant alleles in this Asian population. Alleles *4 and *14 were not found in this patient group.</td>
<td>Author’s conclusion: ”The CYP2D6 genotype did not affect the C/D ratios of fluvoxamine. The mean C/D ratio of fluvoxamine in smokers was reduced by more than 30% in comparison with that in non-smokers, although this was not statistically significant.”

C_{ss} in comparison with *1/*1:
IM: 158%</td>
</tr>
<tr>
<td>ref. 3
Suzuki Y et al. Polymorphisms in the 5-hydroxytryptamine 2A receptor and cytochromeP4502D6 genes synergistically predict fluvoxamine-induced side effects</td>
<td>3</td>
<td>97 patients were treated with fluvoxamine for 12 weeks (initial dose 25 mg/day, then gradual increase to maximum 200 mg/day based on response). Response and the presence or absence of side effects were assessed after 1 week, after 2 weeks and then every 2 weeks. Assessed side effects were nausea, vomiting, anorexia, diarrhoea, stomachache (gastrointestinal side effects), dry mouth, constipation, sleepiness, irritable mood, anxiety, insomnia, headache and dizziness (not</td>
<td>Author’s conclusion: ”Both the A-1438G polymorphism of the 5-HT2A receptor gene and the CYP-2D6 gene polymorphism had significant effects on the inci-</td>
</tr>
</table>

<table>
<tr>
<td>in Japanese depressed patients. Neuropsychopharmacology 2006;31:825-31. PubMed PMID: 16205777.

ref. 3, continuation</td>
<td>IM: B</td>
<td>gastro-intestinal side effects). Because gastrointestinal symptoms can be symptoms of depression as well as side effects, they were not evaluated as side effects when the item gastrointestinal symptoms” on the rating scale for depression became worse compared to the last visit. Relevant co-medication and smoking were not excluded.

Genotyping:
- 75x EM
- 22x IM

Results:
<table>
<tr><td colspan="2">Risk of developing a gastro-intestinal side effect in comparison with EM (incidence = 49% of patients):</td></tr>
<tr><td>IM</td><td>HR = 1.821 (95% CI: 1.019-3.254) (S)</td></tr>
</table>

<table>
<tr><td>IM versus EM:</td></tr>
<tr><td>No difference in:
- incidence of discontinuation (NS)
- onset weeks, onset doses, onset concentrations and cumulative numbers of gastrointestinal side effects (NS).
Both the onset dose (58.8 versus 64.9 mg/day) and the onset concentration (27.4 versus 29.7 ng/ml) were low. Thus, the onset concentration for gastro-intestinal side effects was lower than the therapeutic threshold of 61.4 ng/mL postulated by the authors (see Suzuki 2011).
- incidence of all side effects (NS)</td></tr>
</table>

NB: Alleles *5 and *10 were genotyped. These are the most prevalent variant alleles in this Asian population.</td>
<td>dence of gastrointestinal side effects.”</td>
</tr>
<tr>
<td>ref. 4
Gerstenberg G et al. Effects of the CYP 2D6 genotype and cigarette smoking on the steady-state plasma concentrations of fluvoxamine and its major metabolite fluvoxamino acid in Japanese depressed patients. Ther Drug Monit 2003;25:463-8. PubMed PMID: 12883230.</td>
<td>4

IM: AA</td>
<td>49 patients were treated with fluvoxamine for 6 weeks (50 mg/day in week 1, 100 mg/day in week 2 and 200 mg/day in week 3-6). Relevant co-medication was excluded. Smoking was not excluded (34 patients were non-smokers, 15 smoked ≥ 10 cigarettes/day), but had no significant effect on the plasma concentration. Plasma concentrations were determined in week 4 and corrected to the mean body weight (56.1 kg).

Genotyping:
- 12x gene dose 2 (*1/*1)
- 27x gene dose 1-1.5 (22x *1/*10, 5x *1/*5)
- 10x gene dose 0.5-1 (7x *10/*10, 3x *5/*10)

Results:
<table>
<tr><td colspan="2">Body weight-corrected plasma concentration in comparison with gene dose 2 (144.2 ng/ml):</td></tr>
<tr><td>gene dose 1-1.5</td><td>gene dose 0.5-1</td></tr>
<tr><td>x1.24</td><td>x1.17</td></tr>
<tr><td colspan="2">NS for gene dose 2 versus gene dose 1-1.5 versus gene dose 0.5-1</td></tr>
</table>

<table>
<tr><td>Other results:</td></tr>
<tr><td>- There was a trend for a decrease in the plasma concentration of the metabolite fluvoxamino acid with decreasing gene dose (p = 0.0554) (NS), which became significant in stepwise multiple regression (S). The ratio fluvoxamino acid/fluvoxamine decreased with decreasing gene dose (S). This suggests that CYP2D6 is involved in metabolising fluvoxamine into fluvoxamino acid.</td></tr>
</table>

NB: Alleles *3, *4, *5 and *10 were genotyped. These</td>
<td>Author’s conclusion: ”The present study suggests that the CYP 2D6 genotype and cigarette smoking have no major impact on the C_{ss} of fluvoxamine, though CYP 2D6 is involved in the demethylation of fluvoxamine.”

C_{ss} in comparison with *1/*1:
IM: 117%</td>
</tr>
</table>

ref. 4, continuation		are the most prevalent variant alleles in this Asian population. Alleles *3 and *4 were not found in this patient group.	
ref. 5 Gerstenberg G et al. Relationship between clinical effects of fluvoxamine and the steady-state plasma concentrations of fluvoxamine and its major metabolite fluvoxamino acid in Japanese depressed patients. Psychopharmacology (Berl) 2003;167:443-8. PubMed PMID: 12682708.	4 IM: AA	Clinical effects were determined for the patients in Gerstenberg, Ther Drug Monit 2003. Depressive symptoms were measured at weeks 0, 1, 2, 4 and 6 with the Montgomery Åsberg Depression Rating Scale (MADRS), side effects with the UKU Side Effect Rating Scale. Co-medication with benzodiazepines and smoking were not excluded, but both had no significant association with clinical effects. Results: gene dose 0.5-1 versus gene dose 1-1.5 versus gene dose 2: No difference in: - therapeutic response (final MDRS score, percent improvement, amelioration score, proportion of responders) (all NS) - the incidence of nausea (NS). The incidence of other side effects was very low. Other results: - In stepwise multiple regression, the plasma concentration of fluvoxamine+fluvoxamino acid showed a negative correlation with the final MDRS score and positive correlation with the percent improvement and amelioration score (all S). In logistic regression, the plasma concentration of fluvoxamino acid showed a positive correlation with the chance of being a responder as compared to a nonresponder (S). In univariate analysis, the plasma concentration of fluvoxamine correlated with all the therapeutic response measures (S). The proportion of responders was higher in the patients with a plasma concentration fluvoxamine above 150 ng/mL (S). - There was no association of any of the plasma concentrations with nausea at 4 weeks (NS).	Author's conclusion: "The final MADRS score, percent improvement, amelioration score and proportion of responders were not significantly different among the three genotype groups. …. The incidence of nausea was not different among the three CYP2D6 genotype groups. …. In a separate report (Gerstenberg et al. 2003), we have shown that although CYP2D6 is involved in the demethylation of fluvoxamine to fluvoxamino acid, the CYP2D6 genotype has no major impact on the C_{ss} of fluvoxamine and fluvoxamino acid, probably because of saturation of the enzyme."
ref. 6 Ohara K et al. CYP2D6*10 alleles do not determine plasma fluvoxamine concentration/dose ratio in Japanese subjects. Eur J Clin Pharmacol 2003;58:659-61. PubMed PMID: 12610741.	4 IM: AA	46 patients were treated with fluvoxamine 25-150 mg/day (0.36-3.75 mg/kg body weight per day). Relevant co-medication and smoking were excluded. Genotyping: - 13x *1/*1 - 18x *1/*10 - 15x *10/*10 Results: Dose-corrected and body weight-corrected plasma concentration in comparison with *1/*1 (312.7 ng.kg/mL.mg): *1/*10: x1.059 — *10/*10: x1.027 NS for *1/*1 versus *1/*10 versus *10/*10 NB: Alleles *3, *4, *5 and *10 were genotyped. These are the most prevalent variant alleles in this Asian population. Alleles *3, *4 and *5 were not found in this patient group.	Author's conclusion: "Our results indicate that CYP2D6*10 genotypes do not exert significant effects on fluvoxamine C/D ratio. As CYP2D6 genotypes differ with ethnic background, further studies should be conducted in different populations." C_{ss} in comparison with EM: IM: 99%
ref. 7 Christensen M et al. Low daily 10 mg and 20 mg doses of fluvoxamine inhibit the metabolism of	3	10 healthy volunteers, selected for their CYP2D6 phenotype, received fluvoxamine either as a single dose or daily during 7 days. Doses were 50 mg once and 25 mg twice daily for EM and 25 mg once and 25 mg once daily for PM. Single doses were administered to two additional EM. Relevant co-medication and smoking	Author's conclusion: "No convincing evidence was found that CYP2D6 is an important enzyme for the disposition of

<table>
<tr>
<td>both caffeine (cytochrome P4501A2) and omeprazole (cytochrome P450 2C19).
Clin Pharmacol Ther 2002;71:141-52.
PubMed PMID: 11907488.

ref. 7, continuation</td>
<td>PM: A</td>
<td>were excluded. Plasma concentrations were corrected for dosage by doubling the plasma concentrations for PM.

Phenotyping:
- 5x EM
- 5x PM

Results:
<table>
<tr><td colspan="3">Dose-corrected plasma concentration (C_{ss}) and body weight-corrected oral clearance (Cl_{or}) compared with EM:</td></tr>
<tr><td colspan="3">At the 7th day of daily dosing:</td></tr>
<tr><td></td><td>PM</td><td>C_{ss} (ng/ml) and Cl_{or} (L/h.kg) for EM</td></tr>
<tr><td>C_{ss}</td><td>x1.4 (NS)</td><td>11.8</td></tr>
<tr><td>Cl_{or}</td><td>x0.6 (S)</td><td>1.4</td></tr>
<tr><td colspan="3">After single dosing:</td></tr>
<tr><td>Cl_{or}</td><td>x0.9 (NS)</td><td>1.2</td></tr>
</table>
<table>
<tr><td>PM versus EM:</td></tr>
<tr><td>- no difference in side effects (NS).
Side effects were rather frequent both after the single dose and during the first 2 days of dosing. They were moderate in severity and none of the subjects stopped taking fluvoxamine as a result of side effects.</td></tr>
</table></td>
<td>fluvoxamine. Other factors seem to be more important. A nontherapeutic oral daily dose of fluvoxamine (10-20 mg/day) is sufficient to provide a marked inhibition of caffeine (CYP1A2) metabolism.”

C_{ss} in comparison with EM+IM+UM:
PM: 140%</td>
</tr>
<tr>
<td>ref. 8
Spigset O et al. Relationship between fluvoxamine pharmacokinetics and CYP2D6/CYP2C19 phenotype polymorphisms.
Eur J Clin Pharmacol 1997;52:129-33.
PubMed PMID: 9174682.</td>
<td>3

PM: A</td>
<td>15 healthy volunteers, selected for their CYP2D6 phenotype, received a single dose of fluvoxamine 50 mg. Co-medication and smoking were excluded.

Phenotyping:
- 10x EM
- 5x PM

Results:
<table>
<tr><td colspan="2">AUC compared with EM:</td></tr>
<tr><td>PM</td><td>AUC for EM (ng.h/ml)</td></tr>
<tr><td>x1.31 (S)</td><td>318</td></tr>
</table>
<table>
<tr><td>PM versus EM:</td></tr>
<tr><td>- no difference in:
- Cl_{or} (NS)
- $t_{1/2}$ (NS)</td></tr>
<tr><td>- trend for increase in weight-corrected AUC with decrease in CYP2D6 activity (as measured by the dextrorphan/dextromethorphan ratio) (NS, p = 0.11)</td></tr>
<tr><td>- only the PM with the highest AUC (681 ng.h/ml) developed a side effect (diarrhoea)</td></tr>
</table></td>
<td>Author’s conclusion: ”The results are consistent with a possible minor to moderate role of CYP2D6, but not CYP2C19, in fluvoxamine metabolism.”

$AUC_{single\ dose}$ in comparison with EM+IM+UM:
PM: 131%</td>
</tr>
<tr>
<td>ref. 9
Carrillo JA et al. Disposition of fluvoxamine in humans is determined by the polymorphic CYP2D6 and also by the CYP-1A2 activity.
Clin Pharmacol Ther 1996;60:183-90.
PubMed PMID: 8823236.</td>
<td>3

PM: A</td>
<td>14 healthy volunteers, selected for their CYP2D6 phenotype, received a single dose of fluvoxamine 50 mg. Co-medication was excluded. Smoking was not excluded (5 EM and 1 PM smoked ≥ 12 cigarettes/day).

Phenotyping:
- 10x EM (5 non-smoking)
- 4x PM (3 non-smoking)

Results:
<table>
<tr><td colspan="3">Pharmacokinetic parameters compared with non-smoking EM:</td></tr>
<tr><td></td><td>Non-smoking PM</td><td>AUC (ng.hr/ml), Cl_{or} (L/h.kg) and $t_{1/2}$ (hr) for nonsmoking EM</td></tr>
<tr><td>AUC</td><td>x3.91 (S)</td><td>430.3</td></tr>
</table></td>
<td>Author’s conclusion: ”The disposition of fluvoxamine in humans is associated with the polymorphic CYP2D6 activity, but CYPIA2 also seems to be involved.”

$AUC_{single\ dose}$ in comparison with EM+IM+UM:
PM: 391%</td>
</tr>
</table>

ref. 9, continuation		Cl_{or} x0.19 (S) 2.3 $t_{1/2}$ x2.14 (S) 9.9 AUC, Cl_{or} and $t_{1/2}$ correlated with the CYP2D6 activity (as measured by the 4-hydroxydebrisoquin/debrisoquin ratio) (S). PM versus EM: - no difference in side effects (NS). The smoking PM experienced a paroxysmal supraventricular tachycardia 6 hours after drug intake. However, the symptoms normalised within a few hours.	
ref. 10 SPC Fevarin (fluvoxamine) 14-07-17.		Pharmacokinetic properties: Fluvoxamine is primarily metabolised by CYP2D6 *in vitro*. However, the plasma concentrations of fluvoxamine are not much higher in poor than in extensive CYP2D6 metabolisers.	
ref. 11 SPC Luvox (fluvoxamine), USA, 04-01-17.	PM: A	Drug interactions: While none of the drugs studied for drug interactions significantly affected the pharmacokinetics of fluvoxamine, an in vivo study of fluvoxamine single-dose pharmacokinetics in 13 PM subjects demonstrated altered pharmacokinetic properties compared to 16 “extensive metabolizers” (EM): mean C_{max}, AUC, and half-life were increased by 52%, 200%, and 62%, respectively, in the PM compared to the EM group. This suggests that fluvoxamine is metabolized, at least in part, by CYP2D6. Caution is indicated in patients known to have reduced levels of cytochrome P450 2D6 activity and those receiving concomitant drugs known to inhibit this cytochrome P450 isoenzyme (e.g., quinidine).	$AUC_{single\ dose}$ in comparison with EM+IM+UM: PM: 300%

Risk group	-

Comments:

- Of the kinetic studies, only studies with 3 or more PM, 10 or more IM or 1 or more UM were included in the risk analysis. The contribution of other studies to the evidence was too low. In addition, a later version of Spigset 1997 (Spigset 2001) was not included, because it did not contain relevant new information.
  A case report published in 2016 was not included, because both the antidepressant and antipsychotic in this CYP2D6 PM patient with Kleefstra syndrome were switched (switch from fluvoxamine and quetiapine to desvenlafaxine and olanzapine) and Applied Behaviour Analysis therapies that had been shown to benefit the patient in early childhood were reintroduced simultaneously. For this reason, it is not clear what the contribution was of each of the three therapy changes on the improved clinical outcome.
- Existing guideline:
  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 definition for PM as we do. However, CPIC uses another definition for EM (gene dose 1-2), IM (gene dose 0.5) en UM (gene dose ≥ 2.5). In the summary below, EM, PM, IM and UM are defined according to the KNMP.
  CPIC indicates that data are lacking about the effect of gene dose ≥ 2.5 on fluvoxamine therapy. They state that it might be reasonable to select an alternative SSRI not extensively metabolised by CYP2D6. CPIC classifies the therapeutic recommendation that no recommendation can be given for gene dose ≥ 2.5 due to lack of evidence as optional.
  CPIC indicates that PMs have significantly greater drug exposure to fluvoxamine when compared to gene dose 1-2 (Carrillo 1996 and Spigset 1997). This increase in drug exposure may be a risk factor for drug-induced side effects. The FDA states that fluvoxamine should be used cautiously in patients known to have reduced levels of CYP2D6 activity. To potentially prevent an adverse effect, an alternative SSRI not extensively metabolised by CYP2D6 should be considered for poor metabolisers. If fluvoxamine is warranted, dose extrapolations based on differences in pharmacokinetic parameters between phenotype groups suggest a 30% dose reduction of fluvoxamine (Stingl JC et al. Mol Psychiatry 2013;18:273-87). However, a 30% decrease in dose may not be feasible given the dosage forms. Therefore, a 25-50% dose reduction is recommended. CPIC considers the recommendation for fluvoxamine as optional. The reason is that limited data are available describing the linearity of the dose-concentration relationship and the relation between fluvoxamine concentrations and therapeutic effect and tolerability, because therapeutic drug monitoring is not common for SSRIs.

For gene dose 0.5 no adjustment of fluvoxamine therapy is warranted according to CPIC. Although gene dose 0.5 may be expected to have a modest increase in drug exposure, existing evidence does not support therapy adjustments. CPIC classifies the recommendation to initiate therapy with the recommended initial dose for gene dose 0.5 as moderate. The reason for this is that the literature is difficult to evaluate, because CYP2D6 genotypes are inconsistently categorised as IM or EM. CPIC classifies the recommendation to initiate therapy with the recommended initial dose for gene dose 1-2 as strong.
CPIC provides the following recommendations:
- gene dose ≥ 2,5: no recommendation due to lack of evidence.
- IM (gene dose 0.5 or 1): no action needed.
- PM: consider a 25-50% dose reduction of recommended starting dose and titrate to response or use an alternative drug not metabolised by CYP2D6.

On 16-4-2018, there was not a more recent version of the recommendations present on the PharmGKB- and on the CPIC-site.

Date of the literature search: 9 April 2018.

	Phenotype	Code	Gene-drug interaction	Action	Date
Dutch Pharmaco-genetics Working Group decision	PM	3A	yes	no	14 May 2018
	IM	4B	yes	no	
	UM	-	yes	no	

Mechanism:
Fluvoxamine is predominantly metabolised into inactive metabolites by CYP2D6 and CYP1A2. Fluvoxamine is a potent inhibitor of CYP1A2 and CYP2C19. Thus, fluvoxamine inhibits its own metabolism by inhibiting CYP1A2. This results in a nonlinear dose-concentration relationship. The low capacity of CYP2D6 probably also contributes to this non-linear relationship. Fluvoxamine shows saturation kinetics, particularly at doses above 100 mg/day or plasma concentrations above 150 ng/mL.
A study suggests a plasma concentration fluvoxamine of 61.4 ng/mL as therapeutic threshold (Suzuki Y et al. Concentration-response relationship for fluvoxamine using remission as an endpoint: a receiver operating characteristics curve analysis in major depression. J Clin Psychopharmacol 2008;28:325–8). Another study suggests a plasma concentration fluvoxamine of 150 ng/mL as therapeutic threshold (Gerstenberg, Psychopharmacol 2003).