CYP2C19: fluvoxamine 3509 to 3511

AUC = area under the plasma concentration-time curve, Cl_{or} = clearance after oral administration, 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), PM = poor metaboliser (*2/*2, *2/*3, *3/*3) (absent CYP2C19 enzyme activity), $t_{1/2}$ = 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:
Fluvoxamine is primarily metabolised by CYP2D6 and to a lesser extent by CYP1A2.
None of the three available studies showed an effect of CYP2C19 variants on fluvoxamine exposure. The working group concludes that there is no gene-drug interaction and therefore no adjustment of fluvoxamine therapy required for patients with a CYP2C19 variant (no/no-interactions).
You can find an overview of the observed kinetic 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.

The table below uses the KNMP nomenclature for EM, PM, IM and UM. As a result, the definitions of EM, PM, IM and UM in the table below can differ from the definitions used by the authors in the article.

Source	Code	Effect	Comments
ref. 1 Jan MW et al. Pharmacokinetics of fluvoxamine in relation to CYP2C19 phenotype and genotype. Drug Metabol Drug Interact 2002;19:1-11.	3 PM: AA	13 volunteers (9x EM#, 4x PM (4x *2/*2)) received single doses of 100 mg of fluvoxamine. All PM patients were CYP2D6 EM. No relevant co-medication or caffeine, no smokers. PM versus EM: - No difference in AUC and $t_{1/2}$ Note: genotype only known for the PM patients.	Authors' conclusion: "Fluvoxamine disposition and dosing is unlikely to be affected by CYP2C19 polymorphism."
ref. 2 Spigset O et al. The major fluvoxamine metabolite in urine is formed by CYP2D6. Eur J Clin Pharmacol 2001;57:653-8.	3 PM: AA	Data from the 5 PM patients in Spigset, 1997 were compared to 28 EM#, all of whom were CYP2D6 EM# (5 from Spigset, 1997 and 23 from other studies with the same study protocol). PM versus EM: - No difference in Cl_{or} Note: genotype unknown.	Authors' conclusion: "There were no significant differences between CYP2C19 PMs and controls."
ref. 3 Spigset O et al. Relationship between fluvoxamine pharmacokinetics and CYP2D6/CYP2C19 phenotype polymorphisms. Eur J Clin Pharmacol	3 PM: AA	15 volunteers (10x EM#, 5x PM) received single doses of 50 mg of fluvoxamine. 5 of the EM# and 0 of the PM were CYP2D6 PM. No co-medication or caffeine, no smokers. PM versus EM: - No difference in AUC, $t_{1/2}$ and Cl_{or}, also not after correction for CYP2D6 phenotype Note: genotype unknown.	Authors' conclusion: "The results are consistent with a possible minor to moderate role of CYP2D6, but not CYP2C19, in fluvoxamine metabolism."

1997;52:129-33.			

[#] Phenotyping did not distinguish between EM, IM and UM. EM[#] is therefore equal to EM+IM+UM.

Risk group	--

Comments:

- Possible relationship between CYP2C19 polymorphisms and depression
  - Jukić MM et al. Elevated CYP2C19 expression is associated with depressive symptoms and hippocampal homeostasis impairment. Mol Psychiatry 2017;22:1155-1163. PubMed PMID: 27895323.
    This publication is from the same group as Sim 2010.
    In a cohort of 3849 urban African-Americans of low economic status, the 123 CYP2C19*2/*2 subjects had a decrease in major depressive disorder prevalence compared to the other subjects with at least one active CYP2C19 allele (23% versus 32%) (S). In addition, there was a trend for a lower Beck's Depression Inventory (BDI) score in the CYP2C19*2/*2 subjects compared to the other subjects (p = 0.074). However, the lifetime stress exposure was much larger in the African-American cohort compared with the previously analysed Swedish cohort (Sim 2010), thereby increasing the BDI score variability. After the most traumatized subjects (perceived stress scale score at higher quartile and above) were exempted from the analysis to better match the two samples, the BDI score reduction was significant (effect size = - 2.05 (-24.61%)) (S).
    In order to test whether the CYP2C19 genotype influences suicidality in patients with major depressive disorder, CYP2C19 genotype was tested as a predictor for suicide intent in 209 suicide attempters with major depressive disorder. As there were only two CYP2C19*2/*2 allele carriers in the cohort, it was not possible to test whether this genotype affects Beck's suicide intent scale-objective circumstances (SIS-OS) score. However, in a complementary exploratory analysis, the SIS-OS score seemed to vary between different CYP2C19 genotypes with a decrease for *2/*2 versus *1/*1 versus *1/*2 versus *2/*17 versus *17/*17 versus *1/*17. Further analysis showed that SIS-OS score was not significantly affected by the presence of the CYP2C19*2 allele, whereas it was significantly increased in CYP2C19*17 allele carriers (119 versus 90 subjects, effect size = +1.36 (+25.69%)) (S). Since the score was lower for the 8 patients with genotype *17/*17 compared to the patients with genotype *1/*17, this significant effect seemed to be mainly driven by the *1/*17 genotype. The classification of the suicide attempters to severe (SIS-OS score at higher quartile and above) and non-severe, yielded a higher frequency of patients with *17 allele among severe suicide attempters (S).
    The authors conclude that the CYP2C19*2/*2 genotype associates with a phenotype more resilient to major depressive disorder and that the CYP2C19*17 allele may be a risk allele for suicidality in major depressive disorder. They indicate that a major limitation of the suicidality study is the absence of information regarding the individuals' drug treatment and their drug plasma levels. Therefore, it was not possible to determine whether the observed relationship was caused by endogenous or drug-metabolic CYP2C19-mediated effects.
  - Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium. A mega-analysis of genome-wide association studies for major depressive disorder. Mol Psychiatry 2013;18:497-511. PubMed PMID: 22472876.
    A mega-analysis of genome-wide association studies found no significant association between the risk of depression and CYP2C19.
  - Sim SC et al. Association between CYP2C19 polymorphism and depressive symptoms. Am J Med Genet B Neuropsychiatr Genet. 2010;153B:1160-6.
    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.

Date of literature search: 5 April 2018.

	Phenotype	Code	Gene-drug interaction	Action	Date
Dutch Pharmacogenetics Working Group decision	PM	3 AA	no	no	14 May 2018
	IM	--	no	no	
	UM	--	no	no	

Mechanism:
Fluvoxamine is primarily metabolised by CYP2D6 and to a lesser extent by CYP1A2.