CYP2C19: moclobemide 1991 to 1993

AUC = area under the concentration-time curve, Cl_{or} = oral clearance, IM = intermediate metaboliser (*1/*2, *1/*3, *17/*2, *17/*3) (reduced CYP2C19 enzyme activity), MR = metabolic ratio, NM = normal metaboliser (*1/*1, *1/*17) (normal CYP2C19 enzyme activity), NS = non-significant, PM = poor metaboliser (*2/*2, *2/*3, *3/*3) (absent CYP-2C19 enzyme activity), S = significant, SmPC = Summary of Product Characteristics, $t_{1/2}$ = half-life, UM = ultrarapid metaboliser (*17/*17) (elevated CYP2C19 enzyme activity)

Brief summary and justification of choices:
Moclobemide is primarily converted by CYP2C19 to the C-oxidised metabolite Ro 12-8095. Moclobemide is a CYP2C19 inhibitor and thus, inhibits its own metabolism.
The two available studies showed an increase in AUC or decrease in clearance of moclobemide in healthy volunteers with absent CYP2C19 activity (CYP2C19 poor metabolisers) (Yu 2001 (8 PM) and Gram 1995 (7 PM)). The increase in A|UC is confirmed in the SmPC of moclobemide. However, in case of repeated dosing, the exposure increase is modest (approximately 1.5 times higher) (Gram 1995 and SmPC Moclobemide Mylan 2022). In addition, as far as known, the altered kinetics in PM patients do not lead to an increased incidence of side effects. According to the 'Bonnet U. CNS Drug Rev 2003;9:97-140' review, there seems to be a relationship between plasma concentration and side effects of moclobemide. However, this is not confirmed in Gram 1995. As the latter study involved monotherapy, this study does not provide information on the possible increase in the risk of serotonin syndrome. Because of the altered kinetics combined with the lack of evidence for a clinical effect, the KNMP Pharmacogenetics Working Group concludes that there is a gene-drug interaction, but adjustment of therapy is not required (yes/no-interactions).
You can find a overview of the observed effects in the background information text of the gene-drug interactions in 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 NM, PM, IM and UM. As a result, the definitions of NM, 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 Yu KS et al. Effect of omeprazole on the pharmacokinetics of moclobemide according to the genetic polymorphism of CYP2C19. Clin Pharmacol Ther 2001;69:266-73.	3 PM: A	16 healthy volunteers (8x NM, 8x PM (5x *2/*3, 3x *2/*2)) received 300 mg single doses of moclobemide. PM versus NM: - The AUC increased from 12.98 to 45.98 µg.hour/mL (S by 254%) - Cl_{or} decreased from 29.1 to 6.8 L/hour (S by 77%) - The $t_{1/2}$ increased from 2.43 to 7.56 hours (S by 211%) - The AUC_{24h} ratio (Ro 12-8095 metabolite/moclobemide) decreased from 121.85 to 25.30 (S by 79%) - There was no significant decrease in the AUC_{24h} ratio (Ro 12-5637 metabolite/moclobemide) The AUC_{24h} was not significantly different between *2/*3 and *2/*2 (40.78 versus 41.14 µg.hour/mL).	Authors' conclusion: "Our results show that CYP2C19 is an important enzyme in the elimination of moclobemide." Single dose, AUC versus NM: PM: 354%
ref. 2 Gram LF et al. Moclobemide, a substrate of CYP2C19 and an inhibitor of CYP2C19, CYP2D6,	3	15 healthy volunteers (8x NM#, 7x PM; all CYP2D6 NM) received 300 mg single doses of moclobemide or 600 mg/day for 7 days. PM versus NM: - Median Cl_{or} decreased from 43.2 to 16.1 L/hour	Authors' conclusion: "The panel difference in average steady-state levels was less than a factor two. A panel difference of this small

and CYP1A2: a panel study. Clin Pharmacol Ther 1995;57:670-7. **ref. 3, continuation**	PM: A	after the single dose (S by 63%) and from 22.1 to 13.4 L/hour in steady state (S by 39%) - The median $t_{1/2}$ increased from 1.8 to 4.0 hours after the single dose (S by 122%) and from 2.7 to 5.1 hours in steady state (S by 89%) - There was a lower non-linear increase in plasma concentration after multiple doses: the median AUC ratio (steady state/single dose) increased from 1.98 to 1.31 (S by 34%) and the median $t_{1/2}$ ratio (steady state/single dose) decreased from 1.55 to 1.20 (S by 23%) - The median AUC ratio (Ro 12-8095 metabolite/moclobemide) in steady state decreased from 0.45 to 0.23 (S by 79%) - There was no significant decrease in the AUC ratio (Ro 12-5637 metabolite/moclobemide) in steady state According to the article, volunteers were regularly asked to report side effects, but the article does not provide data on side effects. Note: genotype unknown	size is unlikely to have any clinical consequences." Single dose, Cl_{or} versus NM: PM: 37% Multiple dose, Cl_{or} versus NM: PM: 61%
ref. 3 SmPC Moclobemide Mylan 13-07-22.	0 PM: A	<u>Pharmacokinetics</u>: Approximately 2% of the White population and 15% of the Asian population are 'poor metabolisers' with regard tot the oxidative hepatic metabolism via the cytochrome P450 2C19 iso-enzyme. The maximum plasma concentration (Cmax) and the area under the concentration-time curve (AUC) are approximately 1.5 times higher in 'poor metabolisers' compared to normal metabolisers receiving the same moclobemide dose.	AUC versus NM: PM: 150%

[#] Phenotyping generally does not distinguish between IM and NM. NM in these studies is therefore usually equal to IM+NM.

Risk group	CYP2C19 inhibitor usage by IM patients, concomitant usage of serotonergic medication

Comments:

- <u>Possible relationship between CYP2C19 polymorphism 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.
  In a group of 1472 Europeans older than 44 years (1017x NM (637x *1/*1, 380x *1/*17), 375x IM (290x *1/*2, 85x *2/*17), 35x PM (*2/*2), 45x UM), significantly lower depressive symptoms (measured on the Center of Epidemiologic Studies Depression (CES-D) scale) were found among PM patients than among *1/*1. There was only a difference among people younger than 73 years and in men. The effect size was in the same order of magnitude as that observed between non-users and users of antidepressants. The authors stated that CYP2C19 polymorphisms may have an effect on depressive symptoms in adult Europeans.

Date of literature search: 22 September 2022.

	Phenotype	**Code**	**Gene-drug interaction**	**Action**	**Date**
KNMP Pharmacogenetics Working Group decision	PM	3 A	Yes	No	14 November 2022
	IM	-	Yes	No	
	UM	-	Yes	No	

Mechanism:
Moclobemide is primarily converted by CYP2C19 to the C-oxidised metabolite Ro 12-8095.
N-oxidised metabolites such as Ro 12-5637 are also formed to a lesser extent and independent of CYP2C19.
Moclobemide is a CYP2C19 inhibitor and thus, inhibits its own metabolism.