CYP2C19: esomeprazole 2499 to 2501

amoxi = amoxicillin, AUC = area under the concentration-time curve, CI = confidence interval, clari = clarithromycin, Cl_{or} = oral clearance, eGFR = estimated glomerular filtration rate, esome = esomeprazole, GERD = gastroesophageal reflux disease, Hp = Helicobacter pylori, IM = intermediate metaboliser (*1/*2, *1/*3, *2/*17, *3/*17) (reduced CYP-2C19 enzyme activity), lanso = lansoprazole, metro = metronidazole, MR = metabolic ratio, NM = normal metaboliser (*1/*1, *1/*17) (normal CYP2C19 enzyme activity), NS = non-significant, ome = omeprazole OR = odds ratio, panto = pantoprazole, PM = poor metaboliser (*2/*2, *2/*3, *3/*3) (absent CYP2C19 enzyme activity), PPI = proton pump inhibitor, rabe = rabeprazole, S = significant, SmPC = Summary of Product Characteristics, UM = ultra-rapid metaboliser (*17/*17) (elevated CYP2C19 enzyme activity), RR = relative risk.

Brief summary and justification of choices:

Esomeprazole is primarily metabolised by CYP2C19, producing inactive hydroxy and desmethyl metabolites. In addition to this, esomeprazole is converted by CYP3A4 to esomeprazole sulfone. Esomeprazole is an inhibitor of CYP2C19 and CYP3A4 and thereby of its own metabolism.

The SmPCs report a difference in the AUC for patients with absent CYP2C19 activity (poor metabolisers or PM) versus patients with either normal and/or diminished CYP2C19 activity (normal metabolisers (NM) and/or intermediate metabolisers (IM)). However, this difference does not necessitate a dose adjustment. Most articles in literature support the absence of a significant clinical effect of CYP2C19 genotype.

IM and PM: For PM, 9 of 11 articles on eradication of Helicobacter pylori (including three meta-analyses of 12, 3, and 2 studies, respectively) did not show a significant difference with NM (Morino 2021, Fu 2021, Lee 2014, Tang 2013, Lee 2010, Kang 2008, Miehlke 2008, Miehlke 2006, and Sheu 2005). Of the two articles showing a better Helicobacter pylori eradication for PM (Kuo 2009 and Zhao 2022), Zhao 2022 was a meta-analysis of 6 studies. However, the study with the largest effect for PM included in this meta-analysis, which was also the largest included study with 38% of the total number of PM, investigated dual and quadruple therapy. So, the results of this meta-analysis provide little information on the effect of PM in triple therapy, which is the standard Helicobacter pylori therapy in the Netherlands. For IM, all 10 articles (including four meta-analyses of 12, 6, 3, and 2 studies, respectively) did not show a significant difference (Zhao 2022, Morino 2021, Fu 2021, Tang 2013, Lee 2010, Kuo 2009, Kang 2008, Miehlke 2008, Miehlke 2006, Sheu 2005). 1 of 3 studies on reflux oesophagitis showed a significantly higher incidence of maintained symptomatic response at 1 month for IM and PM compared to NM (Sheu 2008). However, there was no significant difference at 6 months and in the incidence of complete healing of reflux oesophagitis. The other two studies did not find a significant effect (Hsu 2015 and Schwab 2005). No studies were found for peptic ulcer. An increase in side effects for IM and PM or shorter time to a 30% decrease in eGFR for PM was not observed (Miehlke 2008 and Fukui 2024).

Because of the observed kinetic effect, the KNMP Pharmacogenetics Working Group concluded that there is a gene-drug interaction. However, the KNMP Pharmacogenetics Working Group consider the evidence insufficient that this kinetic effect leads to a clinical effect and thus a need for action (yes/no-interactions).

UM: There are few data on patients with an enhanced CYP2C19 activity (ultrarapid metabolisers (UM, *17/*17)) or on the *17-variant leading to enhanced activity. A study with 3 UM and 4 patients with genotype *1/*17 found no significant effect of the CYP2C19 genotype on the AUC of esomeprazole (Deshpande 2016). A study with 2 patients with genotype *1/*17 and 2 patients with genotype *2/*17 found no significant effect of the *17-variant on the time within intragastric pH > 4 on day 1 of treatment (Hunfeld 2010). A case of development of esomeprazole-induced agranulocytosis in a UM was reported (Dury 2012). However, there was no evidence for a causal relationship between the genotype of the patient and the agranulocytosis.

Because of the observed kinetic effect for PM, the KNMP Pharmacogenetics Working Group concluded that there is a gene-drug interaction. However, the KNMP Pharmacogenetics Working Group concluded that there is not enough evidence that this results in an effect of UM or *17 on efficacy or on adverse events, and thus a need for action (yes/no-interaction).

Esomeprazole is given at relatively higher doses than omeprazole: the dose is equal to or for some indications up to twice as high as the omeprazole dose, of which it is the S-isomer. This indicates that the dose of the S-isomer, which has a lower clearance and a higher effectiveness than the R-isomer, is two to four times as high using esomeprazole compared to using omeprazole. In addition, the S-isomer is less influenced by CYP2C19. The effect of the CYP2C19 phenotype on efficacy is therefore less predominant for esomeprazole than for omeprazole.

You can find a detailed overview of the observed kinetic and clinical effects in the background information text of the gene-drug interactions in 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 follows the KNMP definitions for NM, PM, IM and UM. The definitions of NM, PM, IM and UM used in the table below may therefore differ from the definitions used by the authors in the article.

Unless indicated otherwise, results are presented as follows: NM : IM (S or NS versus NM) : PM (S or NS versus NM)

For the period after January 2010, references are listed based on the date of publication only. For the period before, GERD- references are listed first, followed by Hp-references.

Source	Code	Effect	Comments
ref. 1, treatment > 30 days Fukui R et al. Relationships of proton pump inhibitor-induced renal injury with CYP2C19 polymorphism: a retrospective cohort study. Clin Pharmacol Ther 2024;115:1141-51. PMID: 38258325.	3 PM: AA	176 patients were treated with esomeprazole for at least 30 days. Follow-up was for 180 days after treatment initiation. Administration of esomeprazole was for a period of 32-3,727 days (median 404 and 528 days for non-PM and PM, respectively, so longer than the follow-up period). Non-PM patients were more often male than PM patients (84% versus 58%) and there was a significant difference in smoking rates between non-PM and PM patients (percentages smokers/non-smokers/ever smokers 19/30/51 versus 22.5/55/22.5). Patients were excluded if they had a history of kidney disease, received dialysis or continuous haemodialysis and filtration during the observation period, had a very high eGFR (> 125 mL/min/1.73 m^2), or had muscle weakness. Co-medication with CYP2C19 inhibitors and inducers, and with drugs affecting kidney function was not excluded. Neither was the use of other PPIs within 7 days before the start of esomeprazole. Genotyping: - 60x NM - 85x IM - 31x PM Results: PM versus IM+NM: time to a 30% decrease in eGFR: NS NOTE: Genotyping was for *2, *3, and *17. These are the most important gene variants in this Japanese population.	Authors' conclusion: 'This retrospective study showed that CYP2C19 metabolizer status was associated with the time to a 30% eGFR decrease in patients treated with lansoprazole, but not with esomeprazole, rabeprazole, or vonoprazan.'
ref. 2, Hp Zhao X et al. Effects of CYP2C19 genetic polymorphisms on the cure rates of H. pylori in patients treated with the proton pump inhibitors: An updated meta-analysis. Front Pharmacol 2022;13:938419. PMID: 36278195.	3	Meta-analysis of 6 observational or randomised controlled studies with a total of 1728 patients (720 NM, 761 IM, and 247 PM) with H. pylori infection treated with triple, dual or quadruple therapy with esomeprazole. 4 of the included studies used triple therapy, 1 study with a total of 177 patients (73 NM, 89 IM, and 15 PM) used quadruple therapy and 1 study with a total of 722 patients (301 NM, 326 IM, and 95 PM) divided the patients over dual and quadruple therapy. Esomeprazole doses in the trials were not mentioned. Three of the studies in this meta-analysis were also included in this risk analysis separately (Lee 2014, Miehlke 2008, and Sheu 2005). Of the studies in this meta-analysis, 2 were also included in the meta-analyses by Fu 2021 and Tang 2013, and 1 in the meta-analysis by Morino 2021. Meta-analyses were performed with a random-effects model in case of significant heterogeneity between the studies and with a fixed-effect model in case of low heterogeneity between the studies. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was stan-	Authors' conclusion: 'Carriers of CYP-2C19 loss-of-function variant alleles (IM and PM) exhibit a significantly greater cure rate of H. pylori than noncarriers (NM) regardless of other factors. ..... There was a significantly lower H. pylori cure rate in NM subjects than that in IM subjects when treated with omeprazole and lansoprazole, but not rabeprazole, esomeprazole, or pantoprazole.'

<table>
<tr><td>ref. 2, continuation</td><td>PM: AA#

IM: AA</td><td>dardised.
Considering quality of the included studies, only randomisation and blindness (single and double blindness either to treatment or genotype group) were considered. In addition, the results were not reported.
Publication bias analysis was only performed for all studies (all PPIs), not for the subgroup of esomeprazole studies.

Results:<table><tr><td colspan="2">H. pylori eradication rate compared to NM (eradication in 83.9% of patients):</td></tr><tr><td>PM</td><td>OR = 1.89 (95% CI: 1.16-3.13) (S)</td></tr><tr><td></td><td>The H. pylori eradication rate for PM was 90.7%.</td></tr><tr><td></td><td>Note: the largest effect for PM was found in the study investigating dual and quadruple therapy, which is the largest study included in the meta-analysis (including 38% of the total number of PM in the meta-analysis).</td></tr><tr><td>IM</td><td>NS</td></tr><tr><td colspan="2">For both comparisons, there was no heterogeneity between the studies.</td></tr></table></td><td></td></tr>
<tr><td>ref. 3, Hp
Morino Y et al.
Influence of cytochrome P450 2C19 genotype on Helicobacter pylori proton pump inhibitor-amoxicillin-clarithromycin eradication therapy: a meta-analysis.
Front Pharmacol 2021;12:759249.
PMID: 34721043.</td><td>3

IM: AA
PM: AA</td><td>Meta-analysis of 2 randomised controlled trials with a total of 129 patients (59 NM, 44 IM, and 26 PM) with H. pylori infection treated with esomeprazole/amoxicillin/clarithromycin triple therapy. The esomeprazole dose used was 20 mg (one study) or 40 mg (the other study) twice a day during one week.
One of the studies in this meta-analysis was also included in this risk analysis separately (Sheu 2005).
Both studies in this meta-analysis were also included in the meta-analysis by Fu 2021 and 1 was also included in the meta-analysis by Tang 2013.
Meta-analyses were performed with a random-effects model in case of significant heterogeneity between the studies and with a fixed-effect model in case of low heterogeneity between the studies. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised.
Quality of the included studies was not assessed.
Publication bias analysis was performed by funnel plot only and only for all studies (all PPIs), not for the subgroup of esomeprazole studies.

Results:<table><tr><td colspan="2">H. pylori eradication rate compared to NM (eradication in 79.7% of patients):</td></tr><tr><td>IM</td><td>NS</td></tr><tr><td>PM</td><td>NS</td></tr><tr><td colspan="2">For both comparisons, there was no heterogeneity between the studies.</td></tr></table></td><td>Authors’ conclusion: ‘The cure rate of omeprazole and lansoprazole-containing eradication regimens differed among CYP2C19 genotypes, while that of rabeprazole and esomeprazole-containing regimens was similar.’</td></tr>
<tr><td>ref. 4, Hp
Fu J et al.
The effect of CYP-2C19 gene polymorphism on the eradication rate of Helicobacter pylori by proton pump inhibitors-containing regimens in Asian popu-</td><td>3</td><td>Meta-analysis of 12 Asian studies (8 randomised controlled trials and 4 cohort studies) with a total of 1611 patients (607 NM, 676 IM, and 328 PM) with H. pylori infection treated with triple or quadruple therapy. The esomeprazole dose used was 20 mg twice a day in 7 studies (during 1 week in 5 studies and during 10 days or 2 weeks in 1 study each), 40 mg twice a day in 4 studies (during 1 week in 3 studies and during 10 days in 1 study), and either 20 or 40 mg twice a day during 1 week in the 12th study. Three of the included studies used quadruple therapy and two both triple and</td><td>Authors’ conclusion: ‘Rabeprazole-, esomeprazole- and pantoprazole-based eradication program was less affected by the CYP2C19 polymorphism.’</td></tr>
</table>

<table>
<tr>
<td>lations: a meta-analysis. Pharmacogenomics 2021;22:859-79. PMID: 34414773.

ref. 4, continuation</td>
<td>IM: AA
PM: AA</td>
<td>quadruple therapy. A total of 703 included patients (295 NM, 318 IM, and 90 PM) were treated with quadruple therapy. All included studies were assessed as low risk of bias using the Cochrane bias risk assessment tool (based on scoring low, uncertain or high risk of bias in 7 domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias) or as high or medium quality (scoring > 6 or 4-6 of the maximum of 9 points on the Newcastle-Ottawa Scale, respectively). One of the eight included randomised trials had a low risk of bias in 6 domains and an uncertain risk of selective reporting, three had a low risk of bias in 5 domains and an uncertain risk in 2 domains (allocation concealment and selective reporting in two studies and blinding of outcome assessment and selective reporting in the third), two had a low risk of bias in 4 domains and an uncertain risk in 3 domains (allocation concealment, selective reporting, and either blinding of participants and personnel or other bias), one had a low risk of bias in 4 domains, an uncertain risk in 2 domains (allocation concealment and selective reporting) and a high risk of other bias, and the eighth had a low risk of bias in 3 domains, an uncertain risk in 3 domains (allocation concealment, blinding of participants and personnel, and selective reporting) and a high risk of other bias. Two of the four included cohort studies scored 8 points on the Newcastle-Ottawa Scale, one 7 points and the fourth 6 points.
Three of the studies in this meta-analysis were also included in this risk analysis separately (Lee 2010, Kang 2008, and Sheu 2005).
Of the studies in this meta-analysis, 2 were also included in the meta-analysis by Tang 2013.
Meta-analyses were performed with a random-effects model, but prospective registration of the protocol was not mentioned. The search and selection strategy was transparent and the data extraction was standardised.
Publication bias analysis was only performed for all studies (all PPIs), not for the subgroup of esomeprazole studies. For all PPIs, there was publication bias for the comparison of PM and NM.

Results:
<table>
<tr><td colspan="2">H. pylori eradication rate compared to NM (eradication in 81.2% of patients):</td></tr>
<tr><td>IM</td><td>NS</td></tr>
<tr><td>PM</td><td>trend for a higher eradication rate (p = 0.085) (NS)</td></tr>
<tr><td colspan="2">For both comparisons, there was no heterogeneity between the studies.</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>ref. 5, GERD
Deshpande N et al. Rapid and ultra-rapid metabolizers with CYP2C19*17 polymorphism do not respond to standard therapy with proton pump inhibitors. Meta Gene 2016;9:159-64. PubMed PMID:</td>
<td>4</td>
<td>27 healthy volunteers, selected for their CYP2C19 genotypes, received esomeprazole 40 mg once daily for 5 days. Intragastric pH was determined in 6 patients before start of esomeprazole and 24 hours after the dose on day 5. Relevant co-medication was not explicitly excluded, but volunteers were healthy.

Genotyping:
Kinetic study:
- 3x UM
- 4x *1/*17
- 7x (*1/*1+*2/*17+*3/*17)
Clinical study:
- 1x UM
- 1x *1/*17
- 1x (*1/*1+*2/*17+*3/*17)</td>
<td>Authors’ conclusion: ‘Interestingly, noteworthy differences could not be observed in the intra-gastric pH at baseline and on day 6 in response to administration of esomeprazole or pantoprazole in rapid and ultra-rapid metabolizers who are car-</td>
</tr>
</table>

<table>
<tr>
<td>27419077.

ref. 5, continuation</td>
<td>PM: AA
IM: AA
UM: AA
*1/*17: AA</td>
<td>- 8x IM (*1/*2+*1/*3) - 1x IM (*1/*2+*1/*3)
- 5x PM - 2x PM

Results:
<table>
<tr><td colspan="6">PM versus IM versus (*1/*1+*2/*17+*3/*17) versus *1/*17 versus UM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>*1/*17</td><td>UM</td><td>value for (*1/*1+*2/*17+*3/*17)</td></tr>
<tr><td>AUC at day 5</td><td>x 0.71</td><td>x 0.95</td><td>x 0.52</td><td>x 0.51</td><td>15.92 µg.hr/ml</td></tr>
<tr><td></td><td colspan="4">NS for the trend PM versus IM versus (*1/*1+*2/*17+*3/*17) versus *1/*17 versus UM</td><td></td></tr>
<tr><td>increase in intragastric pH</td><td>x 0.03</td><td>x 0.14</td><td>x - 0.01</td><td>x 0.03</td><td>750%</td></tr>
<tr><td>intragastric pH at day 6 ≥ 4</td><td>no</td><td>yes</td><td>no</td><td>no</td><td>no</td></tr>
<tr><td>intragastric pH at day 6 ≥ 3</td><td>yes</td><td>yes</td><td>no</td><td>no</td><td>yes</td></tr>
</table>
NOTE: Genotyping was for *2 to *10, *12 and *17. Only *2, *3 and *17 were detected in this Indian population.</td>
<td>riers of gain of function polymorphism CYP2C19*17.’

AUC versus (*1/*1+*2/*17+*3/*17):
PM: 71%
IM: 95%
UM: 51%</td>
</tr>
<tr>
<td>ref. 6, GERD
Hsu WH et al. Genetic polymorphisms of CYP2C19 and IL1B have no influence on esomeprazole treatment for mild erosive esophagitis. Kaohsiung J Med Sci 2015;31:255-9. PubMed PMID: 25910560.</td>
<td>3

PM: AA
IM: AA</td>
<td>184 patients with mild erosive reflux oesophagitis were treated with esomeprazole 40 mg per day for 8 weeks. In the following 12 weeks, patients received esomeprazole 40 mg per day only if GERD symptoms recurred and only until symptom relieve. GERD symptoms were assessed with a questionnaire every 4 weeks. Endoscopy was performed before and 20 weeks after start of esomeprazole. 24.5% of patients was infected with H. pylori.
Treatment failure was defined as recurrence of GERD symptoms and/or persistent oesophageal erosion and/or need for anti-secretion medication after the first 8 weeks.
Acid-suppressive agents or antacids in the 2 months prior to endoscopy and NSAID’s were excluded. Other relevant co-medication was not excluded.
Associations were investigated with logistic regression analysis.

Genotyping:
- 60x NM
- 98x IM
- 26x PM

Results:
<table>
<tr><td colspan="4">PM versus IM versus NM:</td></tr>
<tr><td></td><td colspan="2">PM IM</td><td>value for NM</td></tr>
<tr><td>% of patients with complete symptom relief after 8 weeks of treatment</td><td colspan="2">NS for PM versus IM versus NM</td><td>100%</td></tr>
<tr><td>% of patients with symptom relapse after treatment</td><td colspan="2">NS for PM versus IM versus NM</td><td>65%</td></tr>
<tr><td>% of patients with persistent oesophageal erosion</td><td colspan="2">NS for PM versus IM versus NM</td><td>43%</td></tr>
<tr><td>% of patients with treatment failure</td><td colspan="2">NS for PM versus IM versus NM</td><td>77%</td></tr>
</table></td>
<td>Authors’ conclusion: ‘There were no relationships between IL-1b and CYP2C19 in the treatment effect in mild reflux esophagitis.’</td>
</tr>
</table>

<table>
<tr>
<td>ref. 6, continuation</td>
<td></td>
<td>NOTE: Genotyping was for *2 and *3. These are the most important gene variants in this Taiwanese population.</td>
<td></td>
</tr>
<tr>
<td>ref. 7, Hp
Lee JY et al.
Factors affecting first-line triple therapy of Helicobacter pylori including CYP2C19 genotype and antibiotic resistance.
Dig Dis Sci 2014;59:1235-43.
PMID: 24599773.</td>
<td>3

PM: AA</td>
<td>486 patients were treated with triple therapy with esomeprazole 40 mg, amoxicillin 1000 mg and clarithromycin 500 mg twice daily for 1 week.
H. pylori status was determined 4 weeks after treatment.
Co-medication affecting CYP2C19 was not excluded.

Genotyping:
- 184x NM
- 227x IM
- 75x PM

Results:
<table>
<tr><td colspan="2">H. pylori eradication rate compared to NM+IM (eradication in 79.8% of patients):</td></tr>
<tr><td rowspan="2">PM</td><td>NS</td></tr>
<tr><td>The H. pylori eradication rate for PM was 86.7%.</td></tr>
</table>
<table>
<tr><td colspan="2">H. pylori eradication rate compared to NM (eradication in 78.3% of patients):</td></tr>
<tr><td rowspan="2">PM</td><td>x 1.11 (significance not determined)</td></tr>
<tr><td>The H. pylori eradication rate for PM was 86.7%.</td></tr>
<tr><td rowspan="2">IM</td><td>x 1.04 (significance not determined)</td></tr>
<tr><td>The H. pylori eradication rate for IM was 81.5%.</td></tr>
</table>
NOTE: Genotyping was for *2 and *3. These are the most important gene variants in this Korean population.</td>
<td>Authors' conclusion: 'The eradication rates for the PM group were higher than those for the non-PM group with both regimens (esomeprazole and pantoprazole based triple therapy) but without statistically significant differences.'</td>
</tr>
<tr>
<td>ref. 8, Hp
Tang HL et al.
Effects of CYP2C19 loss-of-function variants on the eradication of H. pylori infection in patients treated with proton pump inhibitor-based triple therapy regimens: a meta-analysis of randomized clinical trials.
PLoS One 2013;8:e62162.
PubMed PMID: 23646118.</td>
<td>3

PM: AA
IM: AA</td>
<td>Meta-analysis of 3 randomised controlled trials with in total 302 patients with H. pylori infection treated with triple therapy with esomeprazole. One of the trials used two doses (20 and 40 mg twice daily). The other trials used 40 mg twice daily. Risk of bias was high in one of the included studies and unclear in the other two according to the Cochrane risk of bias tool by the following dominions: randomization method, allocation concealment, blinding, incomplete outcome data addressed and selective reporting.
One of the trials in this meta-analysis was also included in this risk analysis separately (Sheu 2005).
If heterogeneity between the studies was not significant, a fixed effects model was used first. Results were confirmed by using a random effects model. This indicates that the initially used statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised.
Possible publication bias was only analysed if there were more than ten studies included in the meta-analysis, so not for esomeprazole.

Genotyping:
- 108x NM
- 125x IM
- 69x PM

Results:
<table>
<tr><td colspan="2">H. pylori eradication rate compared to NM (eradication in 91% of patients):</td></tr>
<tr><td>PM</td><td>NS</td></tr>
<tr><td>IM</td><td>NS</td></tr>
<tr><td colspan="2">There was no significant heterogeneity between the studies.</td></tr>
</table></td>
<td>Authors' conclusion: 'No significant differences were observed for rabeprazole or esomeprazole across the CYP2C19 genotypes of interest.'</td>
</tr>
</table>

<table>
<tr>
<td>ref. 9, GERD
Dury S et al.
Agranulocytosis induced by proton pump inhibitors.
J Clin Gastroenterol 2012;46:859.
PubMed PMID: 22240865.</td>
<td>2

UM: E</td>
<td>A 20-year-old man with cystic fibrosis developed fever with agranulocytosis (white blood cells $1x10^9$/L; neutrophils < $0.1x10^9$/L) 15 days after start of esomeprazole 40 mg per day for persistent reflux disease. Three days after stopping esomeprazole and initiating antibiotics, white blood cells improved to $2.3x10^9$/L and neutrophils to $0.5x10^9$/L.
Antibiotics were monthly used without agranulocytosis recurrence.
10 days before start of esomeprazole, the man developed agranulocytosis while using omeprazole, which was started 4 years earlier. The man recovered after replacing omeprazole by ranitidine.
The man was *17/*17. The authors hypothesize that the enhanced enzyme activity may have induced an increase of toxic (es)omeprazole metabolites leading to agranulocytosis.</td>
<td>Authors' conclusion:
'We hypothesize that the enhanced enzyme activity may have induced an increase of toxic PPI metabolites leading to agranulocytosis.'</td>
</tr>
<tr>
<td>ref. 10, Hp
Lee VW et al.
Pharmacogenetics of esomeprazole or rabeprazole-based triple therapy in Helicobacter pylori eradication in Hong Kong non-ulcer dyspepsia Chinese subjects.
J Clin Pharm Ther 2010;35:343-50.
PubMed PMID: 20831535.</td>
<td>3

PM: AA
IM: AA</td>
<td>104 patients with non-ulcer dyspepsia and H. pylori were treated with triple therapy with esomeprazole 20 mg twice daily for 1 week.
H. pylori status was determined at least 4 weeks after treatment.
Acid-suppressants, NSAID's or aspirin in the 2 weeks prior to treatment were excluded. Other relevant co-medication was not excluded.
Associations were investigated with logistic regression analysis.
It was calculated that approximately 100 patients were needed for a power of 80% to detect a difference of 30% in the eradication of H. pylori in patients with a CYP2C19 variant.

Genotyping:
- 46x NM
- 46x IM
- 12x PM

Results:
<table>
<tr><td colspan="4">PM versus IM versus NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>value for NM</td></tr>
<tr><td>% of patients with H. pylori eradication</td><td colspan="2">NS for PM versus IM versus NM</td><td>87%</td></tr>
</table>

NOTE: Genotyping was for *2 and *3. These are the most important gene variants in this Chinese population.</td>
<td>Authors' conclusion:
'Success eradication was related to clarithromycin resistance and not CYP2C19 genotype.'</td>
</tr>
<tr>
<td>ref. 11 – GERD
Hunfeld NG et al.
A comparison of the acid-inhibitory effects of esomeprazole and pantoprazole in relation to pharmacokinetics and CYP2C19 polymorphism.
Aliment Pharmacol Ther
2010;31:150-9.</td>
<td>4

IM: AA

*17: AA</td>
<td>18 healthy volunteers, 7x *1/*1, 7x *1/*2, 2x *1/*17, 2x *2/*17, received esome 40 mg/day for 5 days, no relevant co-medication;

*1/*1 versus *1/*2:
- No difference in % time with intragastric pH > 4 for 24 hours on Days 1 and 5 (NS)
- No difference in median intragastric pH on Days 1 and 5 (NS)
- No difference in AUC on Day 1 (2.68 : 4.24 mg.h/L (NS)) and Day 5 (5.10 : 8.22 mg.h/L (NS))

*1 versus *17:
- % time with intragastric pH > 4 for 24 hours on Day 1:
  - Approximately 50 : 38 (NS) for *1/*1 versus *1/*17
  - Approximately 63 : 43 (NS) for *1/*2 versus *2/*17

Note: Genotyping was performed for *2, *3, *4, *5, *6 and *17.</td>
<td>Authors' conclusion:
"In contrast to esomeprazole, pantoprazole metabolism is influenced by CYP2C19 polymorphism."</td>
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ref. 12 – GERD Lou HY et al. Optimal dose regimens of esomeprazole for gastric acid suppression with minimal influence of the CYP2C19 polymorphism. Eur J Clin Pharmacol 2009;65:55-64.	4 IM+PM: AA[#]	9 healthy volunteers, 3x NM, 3x IM (2x *1/*2, 1x *1/*3), 3x PM (1x *2/*2, 1x *2/*3, 1x *3/*3), received successive esome 40 mg once daily or esome 20 mg twice daily or esome 10 mg 4x daily for 7 days, no information on co-medication; pH and AUC were determined on Day 7. NM versus IM versus PM: - Median night-time intragastric pH was < 4 for NM and IM on once daily dosing, but not on twice or four times daily dosing: 1x 40 mg: 3.6 : 3.1 (NS) : 4.9 (NS) 2x 20 mg: 5.6 : 5.5 (NS) : 5.8 (NS) 4x 10 mg: 6.6 : 5.5 (NS) : 5.8 (NS) - Median % time with night-time intragastric pH ≥ 4 was significantly higher for NM on four times daily dosing than on once daily dosing; this was not significant for IM and PM. 1x 40 mg: 34.7 : 29.5 (NS) : 64.4 (NS) 2x 20 mg: 89.2 : 77.0 (NS) : 87.4 (NS) 4x 10 mg: 81.9 : 75.9 (NS) : 88.6 (NS) - Median 24-hour intragastric pH for all genotypes and dosing regimens > 4 was: 1x 40 mg: 4.9 : 4.9 (NS) : 5.4 (NS) 2x 20 mg: 6.3 : 6.0 (NS) : 6.0 (NS) 4x 10 mg: 6.6 : 6.0 (NS) : 5.5 (NS) - Median % time with 24-hour intragastric pH ≥ 4 was significantly higher for NM on four times daily dosing than on once daily dosing; this was not significant for IM and PM. 1x 40 mg: 67.5 : 67.8 (NS) : 73.3 (NS) 2x 20 mg: 92.0 : 84.8 (NS) : 87.7 (NS) 4x 10 mg: 92.3 : 86.3 (NS) : 79.2 (NS) - Non-significant trend towards increased $AUC_{0\text{-}24h}$ (in h*ng/mL): 1x 40 mg: 16208.7 : 21037.5 (NS) : 24059.2 (NS) 2x 20 mg: 11016.0 : 12642.5 (NS) : 20723.2 (NS) 4x 10 mg: 10123.1 : 9887.3 (NS) : 20304.6 (NS) Note: Genotyping was performed for *2 and *3.	Authors' conclusion: "It was confirmed that intragastric pH values and plasma esomeprazole concentrations potentially depended on the CYP2C19 genotype status for treatment with esomeprazole. Dosage regimens of divided doses of 20TD or 10Q4D esomeprazole yielded improved antisecretory effects with a minimal influence of CYP2C19 polymorphisms." $AUC_{0\text{-}24h}$ versus NM: On once daily dosing: IM: 130% PM: 148% On twice daily dosing: IM: 115% PM: 188%
ref. 13 - GERD Sheu BS et al. Body mass index can determine the healing of reflux esophagitis with Los Angeles Grades C and D by esomeprazole. Am J Gastroenterol 2008;103:2209-14.	3 IM: AA[#] PM: AA[#]	125 patients with grade C-D reflux oesophagitis, 58x NM, 40x IM, 27x PM, received esome 40 mg/day for 6 months, co-medication unknown; maintained symptomatic response (no regurgitation and no heartburn for ≥ 7 days) and complete healing rates of reflux oesophagitis (no oesophageal ulcer and no erosive reflux oesophagitis) were determined in the 113 patients who completed the study. NM versus IM versus PM: - Incidence of maintained symptomatic response: - At 1 month: 50.0 : 72.2 (S) : 74.3 (S) - At 6 months: 90.7 : 94.4 (NS) : 95.7 (NS) - Incidence of complete healing of reflux oesophagitis: - At 1 month: 44.4 : 40.0 (NS) : 43.1 (NS) - At 6 months: 70.4 : 67.5 (NS) : 72.4 (NS) Note: The IM patients in this study had a significantly higher BMI and higher incidence of obesity. No corrections were made for this. Obesity is an independent risk factor for failure of complete healing. Note: Genotyping was performed for *2 and *3.	Authors' conclusion: "The endoscopic healing rates of reflux esophagitis grades C and D were similar among patients with different genotypes of CYP2C19 at the 1st month and the 6th month, respectively."
ref. 14 – GERD Li ZS et al. Effect of esomepra-	4	36 healthy volunteers, 9x NM, 19x IM, 8x PM, received esome 40 mg/day for 5 days, no co-medication;	Authors' conclusion: "Those who were PM tended to have

zole and rabepra-zole on intragastric pH in healthy Chinese: an open, randomized cross-over trial. J Gastroenterol Hepatol 2007;22:815-20.	IM: AA PM: AA	NM versus IM versus PM: - % time with intragastric pH > 4: Day 1: 69.69 : 72.64 (NS) : 80.68 (NS) Day 5: 81.33 : 80.12 (NS) : 86.81 (NS) - Median intragastric pH: Day 1: 5.33 : 5.61 (NS) : 5.86 (NS) Day 5: 6.22 : 6.03 (NS) : 6.48 (NS) Note: Genotyping was performed for *2 and *3.	a higher, albeit not statistically signifi-cant, percentage of time with intragastric pH >4 and the medi-an 24-h intragastric pH than those who were NM."
ref. 15 - GERD Schwab M et al. Esomeprazole-induced healing of gastroesophageal reflux disease is unrelated to the genotype of CYP2C19: evidence from clinical and pharmacokinetic data. Clin Pharmacol Ther 2005;78:627-34.	3 IM: AA PM: AA	Case-control study, 205 patients including 105 cases (grade A-B reflux oesophagitis) and 100 controls (healed reflux oesophagitis), 148x NM, 51x IM (*1/*2), 6x PM (*2/*2), 50% Hp-neg and 50% Hp-pos, received esomeprazole 40 mg/day for 4 weeks, co-medication unknown; - No significant difference in % NM in cases and controls, in both univariate and multivariate analyses: 75% of controls and 69.5% of cases had the NM genotype - Multivariate analysis showed that the prevalence of the various CYP2C19 genotypes was no different between cases and controls. Note: % Hp-pos cases was non-significantly different from % Hp-pos controls (OR 1.11, 95% CI 0.639-1.915). Note: Genotyping was performed for *2 and *3.	Authors' conclusion: "In contrast to other PPIs, esomepra-zole-induced healing of GERD is unrela-ted to the CYP2C19 genotype, which can be explained by the metabolic shift to-ward the CYP3A4-mediated pathway."
ref. 16 – Hp Kuo CH et al. Efficacy of levoflo-xacin-based rescue therapy for Helico-bacter pylori infec-tion after standard triple therapy: a ran-domized controlled trial. J Antimicrob Chemother 2009;63:1017-24.	3 PM: AA[#] IM: AA	77 patients who failed eradication therapy with PPI/amoxi/clari, 27x NM, 39x IM (*1/*2 or *1/*3), 11x PM (*2/*2 or *2/*3 or *3/*3), received esome 40 mg twice daily + amoxi 1000 mg twice daily + levofloxacin 500 mg once daily for 1 week, co-medication unknown; - There were significantly more PM patients in the success-ful eradication group than in the failed eradication group. NM and IM patients were not significantly more common in either of the groups - NM patients have a higher risk of eradication failure: RR = 1.75 (95% CI = 1.87-17.72) Note: Genotyping was performed for *2 and *3.	Authors' conclusion: "Logistic regression analysis showed that CYP2C19 homozygous normal metabolizer gentype was an important predictor for eradi-cation failure."
ref. 17 – Hp Kang JM et al. Effect of the CYP-2C19 polymorphism on the eradication rate of Helicobacter pylori infection by 7-day triple therapy with regular proton pump inhibitor dosage. J Gastroenterol Hepatol 2008;23:1287-91.	3 IM: AA PM: AA	137 patients, 56x NM, 65x IM (*1/*2 or *1/*3), 16x PM (*2/*2 or *2/*3), 87% clari-susceptible Hp, received twice daily esome 20 mg + amoxi 1000 mg + clari 500 mg for 1 week, co-medication unknown; NM versus IM versus PM: - Eradication % 89.3 : 84.6 (NS) : 100 (NS) Note: Genotyping was performed for *2 and *3.	Authors' conclusion: "The results of this study suggest that the CYP2C19 geno-type status may play a role in the H. pylori eradication rate in patients receiving pantoprazole or eso-meprazole-based triple therapy."
ref. 18 – Hp Miehlke S et al. One-week once-daily triple therapy with esomeprazole, moxifloxacin, and rifabutin for eradica-tion of persistent Helicobacter pylori	3 IM: AA	96 patients, 66x NM, 25x IM, 4x PM, clari and metro-resis-tant and moxifloxacin and rifabutin-susceptible Hp, received once daily esome 40 mg + moxifloxacin 400 mg + rifabutin 300 mg for 1 week, co-medication unknown; NM versus IM versus PM: - Eradication % 75 : 91 (NS) : 100 (NS) - Trend towards higher eradication % in IM+PM versus NM: OR = 4.41 (95% CI = 0.95-20.5) (NS)	Authors' conclusion: "We found lower H. pylori eradication rates in normal me-tabolizers, however, the difference to intermediate and poor metabolizers did not reach statis-

resistant to both metronidazole and clarithromycin. Helicobacter 2008;13:69-74. **ref. 18, continuation**	PM: AA	- No significant association between the incidence of side effects and CYP2C19 phenotype (NS) - No difference in frequency of NM between patients with 1, 2, 3 or ≥ 4 unsuccessful eradication therapies prior to this study Note: Genotyping was performed for *2 and *3.	tical significance due to the relatively small number of patients. We conclude that CYP2C19 polymorphisms may also affect to some extent esomeprazole-based H. pylori rescue therapy in non-Asian patient populations."
ref. 19 – Hp Miehlke S et al. Randomized trial of rifabutin-based triple therapy and high-dose dual therapy for rescue treatment of Helicobacter pylori resistant to both metronidazole and clarithromycin. Aliment Pharmacol Ther 2006;24:395-403.	4 IM+PM: AA	72 patients, 51x NM, 19x IM (*1/*2), 2x PM (*2/*2), clari- and metro-resistant and amoxi-susceptible Hp, received twice daily esome 20 mg + amoxi 1000 mg + rifabutin 150 mg for 1 week, co-medication was not a significant risk factor for eradication failure; NM versus (IM+PM): - Eradication % 75.5 : 84.2 (NS) Note: Genotyping was performed for *2 and *3.	Authors' conclusion: "CYP2C19 polymorphisms appear to have only a small but nonsignificant influence on the efficacy of this regimen in a Caucasian patient population."
ref. 20 – Hp Sheu BS et al. Esomeprazole 40 mg twice daily in triple therapy and the efficacy of Helicobacter pylori eradication related to CYP2C19 metabolism. Aliment Pharmacol Ther 2005;21:283-8.	3 IM: AA PM: AA	200 patients, 91x NM, 65x IM, 44x PM, 65% clari-susceptible Hp, received twice daily ome 20 mg (n=100) or esome 40 mg (n=100) + amoxi 1000 mg + clari 500 mg for 1 week, unknown whether patients had CYP2C19 inhibitors or inducers as co-medication; NM versus IM versus PM: - Eradication % with esome: 84.8 : 84.8 (NS) : 91.3 (NS) In NM patients, the eradication % with esome was significantly increased versus ome, OR 4.2 (per protocol, 95% CI 1.06-16.65) Note: Genotyping was performed for *2 and *3.	Authors' conclusion: "Esomeprazole 40 mg twice daily for triple therapy may improve the *H. pylori* eradication compared to omeprazole-based therapy, but only for normal metaboli-zers of CYP2C19."
ref. 21 SmPC Nexium (esomeprazole) 17-12-21.	0 PM: AA	Pharmacokinetics: *'Poor metabolisers'* Approximately 2.9 ± 1.5% of the population lacks a functional CYP2C19 enzyme, the so-called 'poor metabolisers'. In these individuals, metabolism is propably predominantly by CYP3A4. After repeated once daily dosing of 40 mg esomeprazole, the mean AUC was approximately 100% higher in 'poor metabolisers' than in those with a good functioning CYP-2C19 enzyme. The mean plasma concentrations were increased by approximately 60%. These findings do not impact the esomeprazole dose.	AUC versus NM+IM: PM: 200% Plasma concentration versus NM+IM: PM: 160%
ref. 22 SmPC Nexium (esomeprazole), USA, 18-07-23.	0	Pharmacogenomics: CYP2C19, a polymorphic enzyme, is involved in the metabolism of esomeprazole. The CYP2C19*1 allele is fully functional while the CYP2C19*2 and *3 alleles are nonfunctional. There are other alleles associated with no or reduced enzymatic function. Patients carrying two fully functional alleles are normal metabolizers and those carrying two loss-of-function alleles are poor metabolizers. The systemic exposure to esomeprazole varies with a patient's metabolism status: poor metabolizers > intermediate metabolizers > normal metabolizers. Approximately 3% of Caucasians and	

ref. 22, continuation	IM: AA PM: AA	15 to 20% of Asians are CYP2C19 poor metabolizers. Systemic esomeprazole exposures were modestly higher (approximately 17%) in CYP2C19 intermediate metabolizers (IM; n=6) compared to normal metabolizers (NM; n=17) of CYP2C19. Similar pharmacokinetic differences were noted across these genotypes in a study of Chinese healthy subjects that included 7 NMs and 11 IMs. There is very limited pharmacokinetic information for poor metabolizers (PM) from these studies. At steady state following once daily administration of esomeprazole 40 mg, the ratio of AUC in poor metabolizers to AUC in the rest of the population (NMs) is approximately 1.5. This change in exposure is not considered clinically meaningful.	AUC versus (NM + IM): PM: 150%

Risk group	-

Comments:

- Of the articles published after January 2010, only articles were included with data on patients/healthy volunteers with the *17-variant or with data on more than 100 patients. Other articles did not add enough to the evidence to be included.
  For the period up to and including January 2010, studies with kinetic endpoints only were not included.
  Studies with eradication therapy based on two or four medicines were not included in the status report, nor studies in which the dose of the PPI was lower than the dose registered for eradication in the Netherlands.
- GERD
  Furuta T et al. Pharmacogenomics 2004;5:181-202:
  "There is evidence of reduced clearance with repeated administrations of PPIs resulting in more profound acid suppression. Therefore, observations after single dose administration cannot be extrapolated to more long-term use." "Although the differences among the various genotypes become smaller with longer duration of use of the PPI, they do not completely disappear." Comment KNMP: this contradicts the Velthuyzen Van Zanten response to the meta-analysis by Padol, see below. The effect appears to be dependent on the PPI. Hunfeld et al., 2010 found an increase in the esomeprazole AUC from Day 1 to Day 5, which was similar for NM and IM patients. A similar increase was not observed for pantoprazole. Sakurai et al., 2007 found no increase in the plasma concentration of lansoprazole from Day 1 to Day 5 following intravenous administration.
- Eradication of Hp
  Meta-analysis [Padol S et al. The effect of CYP2C19 polymorphisms on *H. pylori* eradication rate in dual and triple first-line PPI therapies: a meta-analysis. Am J Gastroenterol 2006;101:1467-75] examining the evidence supporting a relationship between the CYP2C19 genotype and eradication of *H. pylori* in primary care. Eradication percentages for the different PPIs (%) are in the order NM : IM: PM for omeprazole 62.9 : 76.7 : 92.7, for lansoprazole 74.4 : 82.9 : 87.5 and for rabeprazole 77.3 : 85.7 : 80.6.
  Authors' conclusion: "We suggest that the intermediate metabolizer term is accurate at the level of acid inhibition but does not translate into lower *H. pylori* eradication rates. Because only omeprazole is affected by CYP2C19 genotype status, it would be logical to increase the dose for this PPI to determine whether an increased dose could overcome the effect of the CYP2C19 genotypes on eradication rates. This can be done in a Caucasian population. (…) An alternate strategy to optimize *H. pylori* eradication would be to use first-line treatments that do not show CYP2C19 polymorphism dependence on eradication rates. According to our meta-analysis, eradication treatments with lansoprazole and rabeprazole fulfil this criterion."
  In a response to the meta-analysis by Padol et al., Velthuyzen van Zanten S and Thompson K [Should the presence of polymorphisms of CYP2C19 enzymes influence the choice of the proton pump inhibitor for treatment of *Helicobacter pylori* infection? J Gastroenterol 2006;101:1476-78] made the following comment: the clearance of a PPI reduces with extended use, resulting in greater suppression of acid secretion. Therefore, results for a single dose cannot simply be extrapolated to long-term use.
- **Other guidelines**:
  - Lima JJ et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2C19 and proton pump inhibitor dosing. Clin Pharmacol Ther 2021;109:1417-23. PMID: 32770672.
    CPIC uses the same definition of UM as we do. However, CPIC uses a different definition for NM (only *1/*1). CPIC created a phenotype rapid metaboliser (RM) for *1/*17. In addition, whereas we do not distinguish between no function and decreased function alleles in our definitions of IM and PM, CPIC does. CPIC assigns genotypes with one reduced function allele and one normal or increased function allele and genotypes with two reduced function alleles to the phenotype 'likely IM'. In addition, CPIC assigns genotypes with one no function allele and one decreased function allele to the phenotype 'likely PM'. The summary below uses the KNMP definitions for NM, PM, IM and UM.

CPIC indicates that there is less evidence linking CYP2C19 genotype with variability in plasma concentrations and effectiveness of second-generation PPIs, like esomeprazole, than of first-generation PPIs, both in terms of number of studies and strength of the association. CPIC indicates that the evidence associating CYP2C19 genotype with esomeprazole plasma concentrations, efficacy, and toxicity was graded as moderate (i.e. evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality or consistency of the individual studies, generalisability to routine practice, or the indirect nature of the evidence) or weak (i.e. evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information). However, in a supplementary table CPIC indicates that the level of evidence is high (i.e. evidence includes consistent results from well-designed, well-conducted studies) for the findings that CYP2C19 PM are not associated with altered H. pylori eradication rate when treated with esomeprazole as compared to IM+NM, and that CYP2C19 is not associated with H. pylori eradication rate when treated with esomeprazole when comparing PM vs IM vs NM. Finally, CPIC indicates that inconsistent findings regarding the effect of CYP2C19 genotype on the pharmacokinetics and therapeutic response to esomeprazole preclude making recommendations for this second-generation PPI (i.e., CPIC level C; no recommendation (i.e. there is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time)).
On 18-6-2024, there was not a more recent version of the recommendations present on the CPIC-site.

Date of literature search: 23 May 2024.

	Phenotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	IM	4 AA[#]	Yes	No	10 September 2024
	PM	4 AA[#]	Yes	No	
	UM	4 E	Yes	No	

[#] If a significant effect was found for PM and IM, then this was a positive effect instead of a negative effect.

Mechanism:
Esomeprazole is primarily metabolised by CYP2C19, producing inactive hydroxy and desmethyl metabolites. In addition to this, esomeprazole is converted by CYP3A4 to esomeprazole sulfone. Esomeprazole is an inhibitor of CYP2C19 and thereby of its own metabolism.