CYP2C19: omeprazole 2505 to 2507

amoxi = amoxicillin, AUC = area under the concentration-time curve, CI = confidence interval, clari = clarithromycin, Cl_{or} = oral clearance, esome = esomeprazole, GERD = gastroesophageal reflux disease, Hp = Helicobacter pylori, IM = intermediate metaboliser (*1/*2, *1/*3, *2/*17, *3/17) (reduced CYP2C19 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).

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:

Omeprazole is primarily converted by CYP2C19 to the inactive hydroxy metabolite. In addition to this, omeprazole is converted by CYP3A4 to omeprazole sulfone. Omeprazole is an inhibitor of CYP2C19 and thereby of its own metabolism. This results in non-linear pharmacokinetics. With doses higher than 40 mg a greater than linear response in AUC occurs.

The literature shows that absent or reduced CYP2C19 activity (poor and intermediate metabolisers (PM and IM)) results in higher plasma concentrations and a higher omeprazole AUC and an increase in CYP2C19 activity (ultra-rapid metaboliser (UM)) in a lower omeprazole AUC.

IM and PM: The result of treatment with omeprazole for each indication was either not significantly different or improved for IM and PM patients. Increased therapeutic effectiveness in IM and PM patients for the indications eradication of Helicobacter pylori (significant in all 5 meta-analyses and 6 of the 10 studies for PM (Zhao 2022, Morino 2021, Fu 2021, Tang 2013, Zhao 2008, Sugimoto, Clin Pharmacol Ther 2006;80:41-50, Sheu 2005, Furuta 2004 , Sapone 2003, Furuta 2001, and Tanigawara 1999) and in 4 of the 5 meta-analyses and 6 of the 11 studies for IM (Zhao 2022, Morino 2021, Fu 2021, Tang 2013, Zhao 2008, Sugimoto, Clin Pharmacol Ther 2006;80:41-50, Gawronska-Szklarz 2005, Sheu 2005, Furuta 2004 , Sapone 2003, and Furuta 2001)), reflux oesophagitis (significant in 1 of the 3 studies for PM (Shirai 2001) and 2 of the 4 studies for IM (Zendehdel 2010 and Shirai 2001)), peptic ulcer/bleeding (significant in 1 of the 5 studies for PM (Sugimoto, Clin Pharmacol Ther 2006;80:539-48) and 2 of the 4 studies for IM (Ando 2008 and Sugimoto, Clin Pharmacol Ther 2006;80:539-48)), and for increasing the gastric pH (significant in 2 of the 4 studies for PM (Shimatani 2003 and Furuta 1999) and 3 of the 5 studies for IM (Hunfeld 2008, Sagar 2000, and Furuta 1999), suggested that the dose in NM patients is actually suboptimal. An increase in side effects was not observed for IM and PM (Helsby 2010, Sugimoto, Clin Pharmacol Ther 2006;80:539-48, and Ohkusa 2005).

Because of the observed kinetic effect, the KNMP Pharmacogenetics Working Group concluded that there is a gene-drug interaction. However, due to the absence of negative effects, it is not useful or necessary to modify the treatment with omeprazole for IM and PM patients (yes/no-interactions).

UM: Significant kinetic consequences were found for UM, but the only two studies investigating clinical consequences (one with 2 UM and 14 *1/*17 and the other reporting 15 UM and 7 *1/*17, but propably including 7 UM and 15 *1/*17) found no effect of UM and *1/*17 on effectiveness (Kee 2022 and Arévalo Galvis 2019). However, decreased therapeutic effectiveness on eradication of Helicobacter pylori and reflux oesophagitis was found for NM patients as compared to IM and PM patients. This effect of reduced effectiveness with an increase in CYP2C19 activity will apply to a greater extent to UM patients.

A case of development of omeprazole-induced agranulocytosis in a UM was reported. However, there was no evidence for a causal relationship between the genotype of the patient and the agranulocytosis.

Because of the observed kinetic effect, the KNMP Pharmacogenetics Working Group concluded that there is a gene-drug interaction. The KNMP Pharmacogenetics Working Group concluded that there is not enough evidence that this results in an effect of UM on side effects. However, there is enough evidence that this will impact the efficacy. For this reason, a dose increase is recommended (yes/yes-interaction). The calculated dose increase is based on the dose increase needed to achieve a similar AUC in NM patients as in 29 PM patients in 5 studies with repeated oral doses, assuming linear pharmacokinetics.

The weighted mean was a dose increase up to 178% of the standard dose (101-677%; median 328%). There was a large variation in the observed AUC difference in the 5 studies. In addition, the SmPC reported a difference of 5 to 10-told for PM compared to NM+IM after repeated dosing, which was much higher than the difference observed between PM and NM in 4 of the 5 studies. The isomer S-omeprazole has a lower clearance than the isomer R-omeprazole and is less influenced by CYP2C19. For esomeprazole, which neither shows a better efficiency or more side effects in PM than in NM, the dose of S-omeprazole is 2- to 4-fold higher than for omeprazole (due to the recommended dose being 1- to 2-fold higher and this dose consisting for 100% instead of 50% of S-omeprazole). Non-linear kinetics might result in a higher than expected increase of AUC with increase of the dose. Despite this, based on the data in the SmPC and the data on esomeprazole, the KNMP Pharmacogenetics Working Group considers it to be save and most appropriate to recommend the median calculated dose increase of 328% instead of the mean calculated dose increase of 178%. The KNMP Pharmacogenetics Working Group translated this to a figure of 300% to be achievable in practice.

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.

Recommendation concerning pre-emptive genotyping, including justification of choices:

The KNMP Pharmacogenetics Working Group considers genotyping before starting omeprazole to be potentially beneficial for drug efficacy. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the KNMP Pharmacogenetics Working Group recommends adhering to the gene-drug guideline.

The clinical implication of the gene-drug interaction scores 2 out of the maximum of 10 points (with pre-emptive genotyping considered to be potentially beneficial for scores ranging from 0 to 2 points):

Dury 2012 describes a UM who developed septic shock due to omeprazole-induced agranulocytosis 4 years after start of omeprazole (severity code E corresponding to CTCAE grade 4). This results in a score of 1 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 (1 point for a clinical effect score D or E (CTCAE grade 3 or 4)).

A negative clinical effect was only found in the case report of Dury 2012. This results in a score of 0 of the maximum of 3 points for the second criterion of the clinical implication score: the level of evidence supporting an associated clinical effect grade ≥ 3 (only points for at least one study with level of evidence score ≥ 3 supporting the associated clinical effect grade ≥ 3). Because the presence of only one case report points to a very rare phenomenon, it also results in a score of 0 of the maximum of 3 points for the third criterion of the clinical implication score: the number needed to genotype (NNG) in the Dutch population to prevent one clinical effect code ≥ D (grade ≥ 3) (only points for NNG ≤ 1000).

The Summary of Product Characteristics (SmPC) does not mention the CYP2C19 UM phenotype, but mentions exposure in CYP2C19 PM to be many times higher than in CYP2C19 NM. 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 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 2009, references are listed based on the date of publication only. For the period before, GERD-references are listed first, followed by references on ulcer/bleeding, Hp-references, and kinetic references.

Source	Code	Effect	Comments
ref. 1, Hpando 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.	3	Meta-analysis of 6 controlled or comparative studies with a total of 613 patients (277 NM, 220 IM, and 116 PM) with H. pylori infection treated with triple therapy with omeprazole. Treatment duration was 7 days in 5 of the included studies and 10 days in the 6th study. Omeprazole doses in the studies were not mentioned. Four of the studies in this meta-analysis were also included in this risk analysis separately (Dojo 2001, Inaba 2002, Sapone 2003, and Sheu 2005). Four of the studies in this meta-analysis were also included in the meta-analyses of Morino 2021, Fu 2021, and Tang 2013, and three in the meta-analysis of Zhao 2008. Meta-analyses were performed with a random-effects model	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

<table>
<tr>
<td>PMID: 36278195.

ref. 1, continuation</td>
<td>PM: AA#

IM: AA#</td>
<td>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.
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.
Possible publication bias was analysed, but only for all studies (all PPIs), not for the subgroup of omeprazole studies.

Results:
<table>
<tr><td colspan="2">H. pylori eradication rate compared to NM (eradication in 66.4% of patients):</td></tr>
<tr><td rowspan="2">PM</td><td>OR = 4.0 (95% CI: 2.0-8.3) (S)</td></tr>
<tr><td>The H. pylori eradication rate for PM was 90.5%.</td></tr>
<tr><td rowspan="2">IM</td><td>OR = 2.4 (95% CI: 1.1-3.8) (S)</td></tr>
<tr><td>The H. pylori eradication rate for IM was 84.1%.</td></tr>
<tr><td colspan="2">For both comparisons, there was no heterogeneity between the studies.</td></tr>
</table>
</td>
<td>NM subjects than that in IM subjects when treated with omeprazole and lansoprazole, but not rabeprazole, esomeprazole, or pantoprazole.’</td>
</tr>
<tr>
<td>ref. 2 - GERD
Kee PS et al. Omeprazole treatment failure in gastroesophageal reflux disease and genetic variation at the CYP2C locus. Front Genet 2022;13:869160. PMID: 35664313.</td>
<td>3</td>
<td>Allele and genotype frequencies in 55 cases who either did not respond to omeprazole or experienced breakthrough heartburn symptoms despite at least 8 weeks of omeprazole (≥ 40 mg/day) were compared to those in a population control. Cases had a median score of 11 (range 5-17 of the maximum of 18) on the GerdQ scale for gastroesophageal reflux disease symptom severity, although 1 laryngopharyngeal reflux case was reported to have a GerdQ score of 0. Patients who presented with heartburn (“burning feeling behind the breastbone”) less than 4 days in a week were only included if they had a GerdQ score of ≥ 8. Patients with gastroesophageal reflux disease symptoms secondary to other underlying clinical conditions were not included. Objective evidence of gastroesophageal reflux disease (typical gastroesophageal reflux disease symptoms in addition to having at least one positive pathological gastroesophageal reflux disease test) was available in a subgroup of 39 cases. The definitions of positive pathological gastroesophageal reflux disease included 24-h oesophageal pH of <4 for ≥ 4.2% of the study time without PPI treatment, ≥ 1.2% with PPI treatment, or close correlation between reported heartburn symptoms and detected reflux events during pH/impedance monitoring. The population control used was the non-Finnish European subset of gnomAD. A study showed a comparable *17 frequency in the New Zealand European control group (the ethnicity of 94.5% of the cases) (control: history of SSRI or SNRI exposure without a history of tolerability problems, n = 105) as in the non-Finnish European subset of gnomAD (*17 frequency of 21% versus 23%). Relevant comedication (comedication known as risk factor for gastroesophageal reflux disease and co-medication known to inhibit or induce CYP2C19) was not excluded.

Genotyping of all cases:
- 24x *1/*1
- 14x *1/*17
- 2x UM
- 15x IM

Results:</td>
<td>Authors’ conclusion: ‘We conclude that omeprazole treatment failure in GERD is associated with CYP2C:TG/TG, but not CYP2C19 *17.’</td>
</tr>
</table>

<table>
<tr>
<td>ref. 2, continuation</td>
<td>UM: AA
*1/*17: AA</td>
<td>
<table>
<tr><td colspan="3">UM and *17 frequency compared to the non-Finnish European subset of gnomAD (23.0% *17 and 5.4% UM):</td></tr>
<tr><td>GERD cases with omeprazole treatment failure</td><td>UM</td><td>*17</td></tr>
<tr><td>all</td><td>NS</td><td>NS</td></tr>
<tr><td>with objective GERD evidence</td><td>NS</td><td>NS</td></tr>
<tr><td>without objective GERD evidence</td><td>NS</td><td>trend for a decrease (p = 0.09) (NS)</td></tr>
<tr><td colspan="3">Note: In two New Zealand reference cohorts with 179 and 129 persons mentioned in this article, the *17 allele frequency was 19% and 18%, respectively. This is numerically lower than in the non-Finnish European subset of gnomAD that was used as a population control in this study.</td></tr>
</table>

Note: Genotyping was for *2, *3, *4, and *17, These are the most important gene variants in this predominantly New Zealand European population.
Note: The authors also analysed the effect of the haplotype characterised by both the CYP2C18 rs2860840 C>T variant and the absence of the CYP2C18 rs11188059 G>A variant. However, because PharmVar mentions only the *17 variant as a variant leading to an increased CYP2C19 enzyme activity, the data on this so called CYP2C:TG haplotype are not included in this summary of the article.
</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 8 randomised controlled trials with a total of 1175 patients (469 NM, 510 IM, and 196 PM) with H. pylori infection treated with omeprazole/amoxicillin/clarithromycin triple therapy. The omeprazole dose used was 20 mg twice a day during one week (seven studies) or during 10 days (one study).
Four of the studies in this meta-analysis were also included in this risk analysis separately (Dojo 2001, Inaba 2002, Sheu 2005, and Arévalo Galvis 2019).
Four of the studies in this meta-analysis were also included in the meta-analyses of Fu 2021 and Tang 2013 and two in the meta-analysis of Zhao 2008.
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.
Possible publication bias was analysed by funnel plot only and only for all studies (all PPIs), not for the subgroup of omeprazole studies.

Results:
<table>
<tr><td colspan="3">H. pylori eradication rate compared to NM (eradication in 79.7% of patients):</td></tr>
<tr><td rowspan="2">IM</td><td colspan="2">NS</td></tr>
<tr><td colspan="2">The H. pylori eradication rate for IM was 81.6%.</td></tr>
<tr><td rowspan="2">PM</td><td colspan="2">RR = 1.66 (95% CI: 1.12-2.46) (S)</td></tr>
<tr><td colspan="2">The H. pylori eradication rate for PM was 85.7%.</td></tr>
<tr><td colspan="3">Heterogeneity between the studies was:
- moderate for the comparison of IM and NM
- absent for the comparison of PM and NM</td></tr>
</table>
</td>
<td>Authors' conclusion: 'The cure rate of omeprazole and lansoprazole-containing eradication regimens differed among CYP2C19 genotypes.'</td>
</tr>
<tr>
<td>ref. 4, Hp
Fu J et al.</td>
<td>3</td>
<td>Meta-analysis of 13 Asian studies (10 randomised controlled trials and 3 cohort studies) with a total of 1895 patients (674</td>
<td>Authors' conclusion: 'Our results also</td>
</tr>
</table>

<table>
<tr>
<td>The effect of CYP-2C19 gene polymorphism on the eradication rate of Helicobacter pylori by proton pump inhibitors-containing regimens in Asian populations: a meta-analysis. Pharmacogenomics 2021;22:859-79. PMID: 34414773.

ref. 4, continuation</td>
<td>IM: AA#

PM: AA#</td>
<td>NM, 908 IM, and 313 PM) with H. pylori infection treated with triple or quadruple therapy. The omeprazole dose used was 20 mg twice a day in all studies (during 1 week in 12 studies and during 10 days in 1 study). One of the included studies with a total of 84 patients (38 NM, 34 IM, and 12 PM) used 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 ten included randomised trials had a low risk of bias in 5 domains and an uncertain risk in 2 domains (allocation concealment and other), five had a low risk of bias in 4 domains and an uncertain risk in 3 domains (allocation concealment, selective reporting, and other in two studies, blinding of participants and personnel, selective reporting, and other in one study, random sequence generation, allocation concealment, and selective reporting in one study, and allocation concealment, blinding of participants and personnel, and selective reporting in one study), two had a low risk of bias in 3 domains, an uncertain risk in 4 domains (allocation concealment, selective reporting, other, and either random sequence generation or blinding of participants and personnel), and two had a low risk of bias in 4 domains, an uncertain risk in 2 domains (allocation concealment and other in one study and blinding of participants and personnel, and selective reporting in the other study) and a high risk of bias in one domain (incomplete outcome data and random sequence generation, respectively). One of the three included cohort studies scored 7 points on the Newcastle-Ottawa Scale and the other two 6 points.
Seven of the studies in this meta-analysis were also included in this risk analysis separately (Tanigawara 1999, Dojo 2001, Furuta 2001, Inaba 2002, Furuta 2004, Sheu 2005, and Sugimoto, Clin Pharmacol Ther 2006;80:41-50).
Five of the studies in this meta-analysis were also included in the meta-analysis of Tang 2013 and four in the meta-analysis of Zhao 2008.
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.
Possible publication bias was analysed only for all studies (all PPIs), not for the subgroup of omeprazole 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 70.8% of patients):</td></tr>
<tr><td rowspan="2">IM</td><td>OR = 2.54 (95% CI: 1.74-3.69) (S)</td></tr>
<tr><td>The H. pylori eradication rate for IM was 86.0%.</td></tr>
<tr><td rowspan="2">PM</td><td>OR = 5.13 (95% CI: 3.08-8.53) (S)</td></tr>
<tr><td>The H. pylori eradication rate for PM was 94.2%.</td></tr>
<tr><td colspan="2">NOTE: The study using quadruple therapy showed the two but lowest influence of IM and the three but lowest influence of PM (OR 1.19 and 3.24, respectively). This indicates that the ORs found in the meta-analysis would be somewhat higher if this study would not have been included.</td></tr>
</table>
</td>
<td>indicated that the efficacies of omeprazole and lansoprazole for treating patients with H. pylori infection were affected by the status of the CYP2C19 genotype.’</td>
</tr>
</table>

<table>
<tr><td>ref. 4, continuation</td><td></td><td>Heterogeneity between the studies was significant and substantial for the comparison of IM and NM and was absent for the comparison of PM and NM.</td><td></td></tr>
<tr><td>ref. 5 - Hp
Arévalo Galvis A et al.
Personalized therapy for Helicobacter pylori: CYP2C19 genotype effect on first-line triple therapy.
Helicobacter 2019;24:e12574.
PMID: 30859680.</td><td>3

genotype-guided versus not-genotype-guided therapy: AA#

UM: AA
IM: AA</td><td>133 patients infected with amoxicillin- and claritromycine-sensitive Helicobacter pylori started treatment with omeprazole/amoxicillin/clarithromycin triple therapy for 10 days with either standard omeprazole doses (20 mg twice a day) (n = 69) or with genotype-guided omeprazole doses (40 mg twice a day for NM and UM, 20 mg 3 times daily for IM, and 20 mg twice daily for PM) (n = 64). 63 patients in the not-genotype-guided group and 59 patients in the genotype-guided group were treated according to protocol.
Verification of H pylori eradication was performed by stool antigen test eight weeks post-treatment.
Patients with serious comorbidities were excluded, but comedication affecting CYP2C19 activity was not.
Based on a type I error of 5%, a type II error of 20%, an eradication rate of 75% in the not-genotype-guided group and of 95% in the genotype-guided group, the required sample size was calculated to be 60 patients per treatment group,

Genotyping:
Genotype-guided group: - 13x UM - 39x NM - 11x IM - 1x PM
Not-genotype-guided group: - 15x UM - 44x NM - 10x IM
Note: the higher numbers of UM than of *1/*17 reported (13 versus 3 in the genotype-guided group and 15 versus 7 in the not-genotype-guided group) suggests that numbers for UM and *1/*17 were interchanged.

Results:
<table>
<tr><td colspan="4">Results for the genotype-guided group compared to the not-genotype-guided group::</td></tr>
<tr><td></td><td>phenotype</td><td></td><td>value for the not-genotype-guided group</td></tr>
<tr><td rowspan="3">eradication rate (intention-to-treat analysis)</td><td>all</td><td>NS</td><td>84.1%</td></tr>
<tr><td>NM+UM</td><td>NS</td><td>83.1%</td></tr>
<tr><td>IM</td><td>NS</td><td>90.0%</td></tr>
<tr><td rowspan="3">eradication rate (per-protocol analysis)</td><td>all</td><td>RR = 1.09 (95% CI: 1.01-1.16) (S)</td><td>92.1%</td></tr>
<tr><td>NM+UM</td><td>trend for an increase (p = 0.05) (NS)</td><td>92.5%</td></tr>
<tr><td>IM</td><td>NS</td><td>90.0%</td></tr>
<tr><td>percentage of patients with adverse events</td><td>all</td><td>NS</td><td>60.9%</td></tr>
<tr><td colspan="4">Note: The most frequent adverse event was altered taste (metallic taste) (17.3% of patients), while 11.3% of patients suffered from diarrhoea.</td></tr>
<tr><td colspan="4">Note: No significant differences in the eradication rates between different CYP2C19 genotypes in both groups were observed.</td></tr>
</table>

Note: Genotyping was for *2, *3, and *17, These are the most important gene variants in this Colombian population.</td><td>Authors' conclusion: 'Effectiveness of guided therapies by susceptibility test was good, yet they can be further improved by customized therapy based on CYP genotype.'</td></tr>
</table>

<table>
<tr>
<td>ref. 6 - kinetics
Park S et al.
Effects of CYP2C19 genetic polymorphisms on PK/PD responses of omeprazole in Korean healthy volunteers.
J Korean Med Sci 2017;32:729-736.
PubMed PMID: 28378544.</td>
<td>3

PM: A
IM: AA</td>
<td>22 healthy volunteers, selected on basis of their CYP2C19 genotype, received omeprazole 20 mg once daily for 8 days. Co-medication was not explicitly excluded, but smoking, alcohol, grape juice and caffeine were.

Genotyping:
- 8x NM
- 6x IM
- 8x PM

Results:
<table>
<tr><td colspan="4">$AUC_{0\text{-}12h}$ compared to NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>value for NM</td></tr>
<tr><td>day 8</td><td>x 2.14 (S)</td><td>x 1.22 (NS)</td><td>1.72 µg.h/ml</td></tr>
<tr><td>day 1</td><td>x 5.12 (S)</td><td>x 1.36 (NS)</td><td>0.71 µg.h/ml</td></tr>
<tr><td colspan="4">For all genotype groups the AUC at day 8 was numerically higher than the AUC at day 1, but the increase was only 0.5% for PM. These data show that the increase with multiple dosing is due to inhibition of CYP2C19.</td></tr>
</table>
Note: Genotyping was for *2, *3 and *17. Volunteers with the *17-variant were excluded from the study.</td>
<td>Authors' conclusion: 'The study demonstrates that CYP-2C19*2 and *3 influence the pharmacokinetics and pharmacodynamics of omeprazole in Korean healthy volunteers.'

AUC versus NM:
IM: 122%
PM: 214%</td>
</tr>
<tr>
<td>ref. 7 - ulcers/bleeding
Chwiesko A et al.
Effects of different omeprazole dosing on gastric pH in non-variceal upper gastrointestinal bleeding: a randomized prospective study.
J Dig Dis 2016;17:588-599.
PubMed PMID: 27518195.</td>
<td>3

*17: AA</td>
<td>41 patients with endoscopically terminated non-variceal upper gastrointestinal bleeding were treated with intravenous omeprazole for 72 hours. 23 patients received a bolus of 80 mg, followed after 5 minutes with a bolus of 40 mg every 12 hours. 18 patients received a bolus of 80 mg, followed by continuous infusion of 8 mg/hour. 58% of patients was infected with H. pylori.
Pharmacokinetics were determined during the first 6 hours of treatment.
Recent treatment with proton pump inhibitors, H_2-receptor antagonists, antacids, steroids, oral contraceptives, clopidogrel, prasugrel, and clarithromycin was excluded, but other relevant co-medication was not.

Genotyping:
<table>
<tr><td>Bolus group</td><td>Infusion group</td></tr>
<tr><td>- 9x *1/*17</td><td>- 1x UM</td></tr>
<tr><td>- 13x *1/*1</td><td>- 7x *1/*17</td></tr>
<tr><td>- 1x IM</td><td>- 6x *1/*1</td></tr>
<tr><td></td><td>- 4x IM</td></tr>
</table>
Results:
<table>
<tr><td colspan="2">(*1/*17 + UM) compared to *1/*1:</td></tr>
<tr><td>intragastric pH at 13 time points (10 minutes to 72 hours) after the 80 mg bolus for each dosing regimen</td><td>NS</td></tr>
<tr><td>% time at pH > 4.0 for each dosing regimen</td><td>NS</td></tr>
<tr><td>% time at pH > 6.0 for each dosing regimen</td><td>NS</td></tr>
<tr><td>$AUC_{0\text{-}6hr}$ for each dosing regimen</td><td>NS</td></tr>
</table>
Note: Genotyping was for *2, *3 and *17.</td>
<td>Authors' conclusion: 'In both groups, CYP2C19 genotypes (*1/*1, *1/*17, *17/*17) had no essential effect on intragastric pH.'</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</td>
<td>3</td>
<td>Meta-analysis of 6 randomised controlled trials with in total 537 patients with H. pylori infection treated with triple therapy with omeprazole. All trials used omeprazole 20 mg twice daily in combination with amoxicillin and clarithromycin. Risk of bias was high in 3 of the included studies, unclear in 2 studies, and low in 1 study according to the Cochrane risk of bias tool by the following dominions: randomization method, allocation concealment, blinding, incomplete outcome data addressed and selective reporting.
Three of the trials in the meta-analysis were also included in</td>
<td>Authors' conclusion: 'Carriage of CYP-2C19 loss-of-function variants is associated with increased H. pylori eradication rate in patients taking PPI-based triple therapies when omepra-</td>
</tr>
</table>

<table>
<tr>
<td>regimens: a meta-analysis of randomized clinical trials. PLoS One 2013;8:e62162. PubMed PMID: 23646118.

ref. 8, continuation</td>
<td>PM: AA#
IM: AA#</td>
<td>this risk analysis separately (Dojo 2001, Inaba 2002 and Sheu 2005).
Three of the trials in this meta-analysis were also included in the meta-analysis of Zhao 2008.
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 omeprazole.

Genotyping:
- 194x NM
- 241x IM
- 102x PM

Results:
<table>
<tr><td colspan="2">H. pylori eradication rate compared to NM (eradication in 73% of patients):</td></tr>
<tr><td>PM</td><td>OR = 4.31 (95% CI: 1.94-9.52) (S)</td></tr>
<tr><td>IM</td><td>OR = 3.04 (95% CI: 1.88-5.13) (S)</td></tr>
<tr><td colspan="2">There was no significant heterogeneity between the studies.</td></tr>
</table>

The authors indicate that the higher cure rate in PM compared to NM, suggests that NMs may need to take a higher-than-standard dose of omeprazole.</td>
<td>zole or lansoprazole is chosen.’</td>
</tr>
<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 septic shock due to agranulocytosis (white blood cells 0.7x10^9/L; neutrophils < 0.1x10^9/L) 4 years after start of omeprazole.
Clinical and biological outcomes improved in 48 hours after stopping omeprazole and initiating ranitidine.
Nine days after stopping omeprazole, esomeprazole 40 mg/day was started. Agranulocytosis recurred 16 days later and the patient recovered after stopping esomeprazole.
Antibiotics were monthly used without agranulocytosis recurrence.
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 - ulcers/ bleeding
Wang L et al. Ilaprazole for the treatment of duodenal ulcer: a randomized, double-blind and controlled phase III trial. Curr Med Res Opin 2012;28:101-9. PubMed PMID: 22070512.</td>
<td>3</td>
<td>156 patients with 1 or 2 endoscopically diagnosed duodenal ulcers with a larger diameter of 0.3-2.0 cm were treated with omeprazole 20 mg once daily for 4 weeks. Hydrotalcite was allowed for severe pain on the first day. 88% of patients was infected with H. pylori.
Ulcer complete healing was defined as transition from an active ulcer to a white scar.
Recent treatment with proton pump inhibitors and use or need of other proton pump inhibitors, NSAIDs, H_2-receptor antagonists, gastromucosal protective agents, gastric acid neutralizers except hydrotalcite, platelet inhibitors, anticoagulants, antidepressants, gastrointestinal regulators, antibiotics, and drugs for relieving spasm and pain were excluded. Co-medication influencing CYP2C19 was not excluded.

Genotyping:
- 51x NM
- 67x IM
- 38x PM

Results:
<table>
<tr><td>Percentage of patients with ulcer complete healing for</td></tr>
</table>
</td>
<td>Authors’ conclusion: ‘The trend of ulcer complete healing rate changing with different CYP2C19 genotypes in the omeprazole group is coincident with the literature though there is no statistically significant difference largely due to its limited sample size, which was designed just for the test of non-inferiority.’</td>
</tr>
</table>

<table>
<tr><td>ref. 10, continuation</td><td>PM: AA
IM: AA</td><td>
<table>
<tr><td colspan="3">PM versus IM versus NM:</td></tr>
<tr><td></td><td></td><td>value for NM</td></tr>
<tr><td>after 2 weeks</td><td>NS</td><td>23.5%</td></tr>
<tr><td>after 4 weeks</td><td>NS</td><td>80.4%</td></tr>
</table>
Note: Genotyping was for *2 and *3. These are the most important gene variants in this Chinese population.
</td><td></td></tr>
<tr><td>ref. 11 - GERD
Zendehdel N et al. Role of cytochrome P450 2C19 genetic polymorphisms in the therapeutic efficacy of omeprazole in Iranian patients with erosive reflux esophagitis.
Arch Iran Med 2010;13:406-12.
PubMed PMID: 20804307.</td><td>3

IM: AA#</td><td>81 patients with erosive reflux esophagitis were treated with omeprazole 20 mg twice daily for 4 weeks. 70% of patients was infected with H. pylori. After completion of treatment, endoscopy was performed in 38 patients.
Complete clinical response was defined as the absence of GERD symptoms after treatment. Endoscopic response was defined as at least one score improvement in the grade of esophagitis (on a 4-grade scale).
Proton pump inhibitors in the preceding 4 weeks were excluded. Other relevant co-medication was not excluded.

Genotyping:
- 58x NM
- 23x IM

Results:
<table>
<tr><td colspan="3">Results compared to NM:</td></tr>
<tr><td></td><td>IM</td><td>value for NM</td></tr>
<tr><td>% of patients with complete clinical response</td><td>x 2.2;
OR = 30.36 (95% CI: 3.83-240) (S)</td><td>43%</td></tr>
<tr><td>% of patients with endoscopic response</td><td>x 1.5 (NS)</td><td>55%</td></tr>
</table>
Note: Genotyping was for *2 and *3. Next to *17, these are the most important gene variants in this Iranian population.</td><td>Authors' conclusion: 'The clinical response and endoscopic healing of esophagitis are both affected by CYP2C19 genotype condition.'</td></tr>
<tr><td>ref. 12 - GERD
Helsby NA et al. Omeprazole-induced acute interstitial nephritis is not related to CYP2C19 genotype or CYP-2C19 phenotype.
Br J Clin Pharmacol 2010;69:516-9.
PubMed PMID: 20573087.</td><td>3

IM: AA
PM: AA</td><td>20 patients with omeprazole-induced acute interstitial nephritis were studied. Patients were treated with omeprazole for a period of 1 week to 8 years. The most prevalent indication for omeprazole was gastroesophageal reflux disease (40% of patients). 90% of the patients was 65 years or older.
Relevant co-medication was not excluded, but there were no indications for relevant co-medication in the patient's records.
The genotype distribution of a reference population was obtained from literature.

Genotyping:
- 15x NM
- 5x IM

Results:
<table>
<tr><td>Genotype distribution of patients with acute interstitial nephritis compared with that of a reference population:</td></tr>
<tr><td>NS</td></tr>
</table>
Note: Genotyping was for *2 and *3. Next to *17, these are the most important gene variants in this New-Zealand population.</td><td>Authors' conclusion: 'The CYP2C19 poor metabolizer genotype was not over represented in patients with omeprazole-induced acute interstitial nephritis.'</td></tr>
<tr><td>ref. 13 - GERD
Saitoh T et al. Influences of CYP-2C19 polymorphism on recurrence of reflux esophagitis during proton pump</td><td>3

IM: AA</td><td>28 patients whose GERD had healed after omeprazole 20 mg/day for 8 weeks (8x NM, 14x IM, 6x PM, 39% Hp-pos) received omeprazole 20 mg/day as maintenance therapy for 6 months, co-medication unknown;

NM versus IM versus PM:
- frequency of recurrence of GERD symptoms (%): 50 : 14</td><td></td></tr>
</table>

inhibitor maintenance therapy. Hepatogastroenterology 2009;56:703-6. **ref. 13, continuation**	PM: AA	(NS) : 17 (NS) For the total study group (45x rabeprazole, 28x omeprazole, 26x lansoprazole), a significantly lower frequency of recurrence of GERD symptoms was found for IM and PM versus NM. Note: Genotyping was performed for *2 and *3.	
ref 14 - GERD Hunfeld NG et al. Effect of CYP2C19 *2 and *17 mutations on pharmacodynamics and kinetics of proton pump inhibitors in Caucasians. Br J Clin Pharmacol 2008;65:752-60.	4 IM: AA [#] *17: AA	H. pylori-negative healthy volunteers received omeprazole 10 mg/day (n=11: 5x *1/*1, 1x *1/*17, 1x *2/*17, 4x *1/*2) or omeprazole 20 mg/day (n=16: 6x *1/*1, 6x *1/*17, 1x *2/*17, 2x *1/*2, 1x *2/*2) for 6 days. *1/*2 versus *1/*1 (10 mg omeprazole): - no significant effect on the percentage of time with intragastric pH > 4 for 24 hours on Days 1 and 6 - omeprazole significantly increased the percentage of time with intragastric pH > 4 on Days 1 and 6 for *1/*2, but not for *1/*1 - non-significant increase in AUC on Days 1 and 6 *1/*17 versus *1/*1 (20 mg omeprazole): - no significant effect on the percentage of time with intragastric pH > 4 for 24 hours on Days 1 and 6. - non-significant reduction in AUC on Days 1 and 6. AUC ratio at day 6 of omeprazole 20 mg/day for PM versus *1/*2 versus *2/*17 versus *1/*1 versus *1/*17: - 3.8 : 3.3 : 1.8 : 1 : 0.77 (value for *1/*1 = 1.11 µg.h/ml) (NS) Note: Genotyping was performed for *2, *3, *4, *5, *6 and *17.	Authors' conclusion: "This study showed that the acid-inhibitory effects of omeprazole in Caucasians were influenced by CYP2C19 status. Due to this effect, single and repeated administration of omeprazole 10 mg in *1/*1 subjects did not provide significant acid-inhibition when compared with baseline." AUC versus NM: PM: 428% IM: 317%
ref. 15 - GERD Ohkusa T et al. Effect of CYP2C19 polymorphism on the safety and efficacy of omeprazole in Japanese patients with recurrent reflux esophagitis. Aliment Pharmacol Ther 2005;21:1331-9.	3 IM: AA PM: AA	119 patients with reflux oesophagitis grade A-D (46x NM, 53x IM, 20x PM, 75x Hp-neg and 44x Hp-pos), received 10-20 mg omeprazole for 6-12 months, no antacid medication, co-medication with an effect on CYP2C19 unknown; NM versus IM versus PM: - no significant difference in the occurrence of side effects between the various genotypes. - healing (%) at 6 months: 85.0 : 83.3 (NS) : 83.3 (NS) - healing (%) at 12 months: 73.1 : 84.0 (NS) : 80.0 (NS) Note: Genotyping was performed for *2 and *3.	Authors' conclusion: "These data clearly indicate that genotype determination of the purpose of dose adjustment is not necessary in Japanese patients undergoing long-term therapy with 1-10 mg of 20 mg omeprazole daily."
ref. 16 - GERD Roh HK et al. Omeprazole treatment of Korean patients: effects on gastric pH and gastrin release in relation to CYP2C19 geno- and phenotypes. Basic Clin Pharmacol Toxicol 2004;95:112-9.	3 IM: AA PM: AA	26 patients with reflux oesophagitis or an ulcer (6x NM, 10x IM (6x *1/*2, 4x *1/*3), 10x PM (4x *2/*2, 4x *2/*3, 2x *3/*3), not tested for Hp), received omeprazole 20 mg/day for 8 days, no relevant co-medication; NM versus IM versus PM: - pH on Day 8: 6.0 : 5.41 (NS) : 6.3 (NS) - gastrin AUC (pM.h): 262 : 255 (NS) : 366 (NS) - AUC omeprazole (nM.h): 8683 : 8451 (NS) : 8747 (NS) - AUC OH-omeprazole (nM.h): 1077 : 1052 (NS) : 381 (S) Note: Genotyping was performed for *2 and *3.	AUC versus NM: IM: 97% PM: 101%
ref. 17 - GERD Shirai N et al. Effects of CYP2C19 genotypic differences in the metabo-	4	15 healthy volunteers (6x NM, 5x IM (4x *1/*2, 1x *1/*3), 4x PM (2x *2/*2, 2x *2/*3), Hp-neg), received omeprazole 20 mg/day for 8 days, no co-medication; NM versus IM versus PM:	

lism of omeprazole and rabeprazole on intragastric pH. Aliment Pharmacol Ther 2001;15:1929-37.	IM: AA[#] PM: AA[#]	- pH on Day 8: 4.1 : 4.7 (S) : 5.9 (S) - AUC (ng.h/mL) on Day 8: 1056.96 : 2417.5 (S) : 7153.0 (S) Note: Genotyping was performed for *2 and *3.	AUC versus NM: IM: 229% PM: 677%
ref. 18 - GERD Sagar M et al. Effects of omeprazole on intragastric pH and plasma gastrin are dependent on the CYP-2C19 polymorphism. Gastroenterology 2000;119:670-6.	3 IM: AA[#] PM: AA	25 patients (11x NM of which 6 Hp-pos, 12x IM (*1/*2) of which 6 Hp-pos, 2x PM (*2/*2) both Hp-pos) received a single dose of 20 mg omeprazole, co-medication unknown: NM versus IM versus PM: - percentage time pH > 4 on Day 8: 37.1 : 72.4 (S) : 93.3 (NS) - gastrin AUC (pM.h) on Day 8, increase versus baseline: 16 : 184 (S) : 172 (NS) Note: Genotyping was performed for *2 and *3.	Authors' conclusion: "Analysis of the CYP2C19 genotype or phenotype in patients considered for long-term treatment may be important to avoid the negative consequences of profound acid inhibition by PPIs in a subgroup of patients with H.pylori infection."
ref. 19 - GERD Furuta T et al. CYP2C19 genotype status and effect of omeprazole on intragastric pH in humans. Clin Pharmacol Ther 1999;65:552-61.	3 IM: AA[#] PM: AA[#]	16 healthy volunteers (6x NM, 4x IM (3x *1/*2, 1x *1/*3), 6x PM (4x *2/*3, 2x *2/*2), 1x Hp-pos), received a single dose of 20 mg omeprazole, no co-medication: NM versus IM versus PM: - mean intragastric pH: 2.14 : 3.30 (S) : 4.47 (S) - gastrin AUC_{0-24} (pg/mL.h): 1569 : 1470 (NS) : 2386 (S) - omeprazole AUC_{0-24} (ng/mL.h): 421 : 1403 (NS) : 5109 (S) Note: Genotyping was performed for *2 and *3.	

ref. 20 - GERD
Shimatani T et al. Effect of omeprazole 10 mg on intragastric pH in three different CYP2C19 genotypes, compared with omeprazole 20 mg and lafutidine 20 mg, a new H2-receptor antagonist. Aliment Pharmacol Ther 2003;18:1149-1157.
	4
	
	IM: AA
	PM: AA[#]
		18 healthy men (6x NM, 6x IM, 6x PM) received omeprazole 10 mg/day or omeprazole 20 mg/day or water for 7 days in a cross-over study, no co-medication.
		
		NM versus IM versus PM:
		- mean intragastric pH after 7 days:
		  - water: 1.6 : 1.6 : 1.7 (NS)
		  - 10 mg omeprazole: 2.0 : 2.5 (NS) : 5.4 (S)
		  - 20 mg omeprazole: 3.7 : 4.4 (NS) : 6.3 (S)
		- percentage time pH > 4 after 7 days:
		  - water: 8 : 11 : 11 (NS)
		  - 10 mg omeprazole: 23 : 24 (NS) : 81 (S)
		  - 20 mg omeprazole: 46 : 56 (NS) : 90 (S)
		
		Note: Genotyping was performed for *2 and *3.
			Authors' conclusion: "Omeprazole 10 mg strongly suppresses acid secretion, but depending on the CYP2C19 genotypes shows greater inter-individual variations in suppression than 20 mg."

ref. 21 - ulcers/ bleeding Ando T et al. Endoscopic analysis of gastric ulcer after one week's treatment with omeprazole and rabeprazole in relation to CYP2C19 genotype. Dig Dis Sci 2008;53:933-7.	3 IM: AA[#] PM: AA	35 patients with peptic ulcers (15x NM, 14x IM, 6x PM) recei-ved omeprazole 20 mg 1x daily for 8 weeks, 89% Hp-pos, no antacid medication, NSAIDs, anticoagulants, corticoste-roids or gastrokinetics, co-medication with an effect on CYP-2C19 unknown. NM versus IM versus PM: - % decrease in the surface of the ulcer after 1 week: 46.3 : 61.7 (S) : 63.2 (NS) Note: Genotyping was performed for *2 and *3.	Authors' conclusion: "The improvement ratio in IM patients was significantly greater than that in NM patients. Similarly, the improvement ratio in PM patients was apparently greater than that in NM patients although the difference was not statistically significant."
ref. 22 - ulcers/ bleeding Sugimoto M et al. Initial 48-hour acid inhibition by intravenous infusion of	4	15 Hp-positive volunteers (5x NM, 5x IM (4x *1/*2, 1x *1/*3), 5x PM (2x *2/*2, 1x *2/*3, 2x *3/*3)) received intravenous ome 20 mg or ome 10 mg + famotidine 10 mg or ome 20 mg + famotidine 20 mg 2x daily for 2 days in a cross-over study, no co-medication;	Authors' conclusion: "This study suggests that the CYP2C19 genotyping test appears to be a useful tool for determining

omeprazole, famotidine, or both in relation to cytochrome P450 2C19 genotype status. Clin Pharmacol Ther 2006;80:539-48.
 	
ref. 22, continuation
	IM: AA[#]
	PM: AA[#]
		NM versus IM versus PM:
		- median intragastric pH on Day 1:
		  - ome 20 mg: 3.9 : 5.8 (S) : 6.1 (S)
		  - ome 10 mg + famotidine 10 mg: 3.6 : 5.2 (S) : 5.5 (S)
		  - ome 20 mg + famotidine 20 mg: 4.8 : 5.8 (S) : 5.8 (S)
		  For all three regimens, NM did not achieve the pH required to allow platelet aggregation and plasma coagulation (pH > 5.5). For IM and PM, this was only the case for ome 10 mg + famotidine 10 mg.
		  For two of the regimens, the median pH for NM remained below the pH at which fibrin clots dissolve (pH <4.0).
		- median intragastric pH on Day 2:
		  - ome 20 mg: 5.3 : 6.2 (S) : 6.6 (S)
		  - ome 10 mg + famotidine 10 mg: 5.9 : 5.7 (NS) : 6.0 (NS)
		  - ome 20 mg + famotidine 20 mg: 5.4 : 5.9 (NS) : 6.0 (NS)
		  For two of the regimens, NM did not achieve the pH required to allow platelet aggregation and plasma coagulation (pH > 5.5).
		- percentage time pH > 4 on Day 1:
		  - ome 20 mg: 58.0 : 86.1 (S) : 92.5 (S)
		  - ome 10 mg + famotidine 10 mg: 49.8 : 79.3 (NS) : 85.1 (NS)
		  - ome 20 mg + famotidine 20 mg: 73.6 : 89.7 (S) : 92.3 (S)
		- percentage time pH > 4 on Day 2:
		  - ome 20 mg: 86.9 : 98.8 (NS) : 99.4 (NS)
		  - ome 10 mg + famotidine 10 mg: 88.4 : 87.5 (NS) : 96.8 (NS)
		  - ome 20 mg + famotidine 20 mg: 87.1 : 98.1 (S) : 97.7 (S)
		- median time to achieve an intragastric pH > 5.5 (in hours):
		  - ome 20 mg: 11.3 : 2.8 (S) : 0.9 (S)
		  - ome 10 mg + famotidine 10 mg: 1.9 : 1.2 (NS) : 1.7 (NS)
		  - ome 20 mg + famotidine 20 mg: 1.2 : 1.0 (NS) : 1.0 (NS)
		- there were no side effects for any of the genotypes
		
		Note: Genotyping was performed for *2 and *3.
			the optimal treatment for the prevention of hemorrhage (or rebleeding) from peptic ulcer diseases.
			We recommend the following intravenous infusion regimens for patients who require intensive gastric acid control in the early post-administration phase: 20 mg omeprazole twice daily in PMs and heterozygous NMs and concomitant infusion of 20 mg omeprazole plus 20 mg famotidine twice daily in homozygous NMs of CYP2C19."

ref. 23 - ulcers/ bleeding Ji S et al. Comparison of the efficacy of rabeprazole 10 mg and omeprazole 20 mg for the healing rapidity of peptic ulcer diseases. J Gastroenterol Hepatol 2006;21:1381-7.	3 PM: AA	53 patients with active peptic ulcers (3x NM, 25x IM, 25x PM) received omeprazole 20 mg 1x daily for 6 weeks, 77% Hp-pos, no antacid medication, anticoagulants, corticosteroids, anticholinergics, antidepressants or oncolytics, co-medication with an effect on CYP2C19 unknown. (NM + IM) versus PM: - % decrease in the surface of the ulcer after 1 week: 48.6 : 50.9 (NS) - % of healed patients after 6 weeks: 87.5 : 86.4 (NS) Note: the NM + IM group consisted primarily of IM Note: Genotyping was performed for *2 and *3.	Authors' conclusion: "CYP2C19 genotypes had no effect on the remaining ratio of peptic ulcers after 1 week and the healing rate of peptic ulcers after 6 weeks."
ref. 24 - ulcers/ bleeding Ando T et al. A comparative study on endoscopic ulcer healing of omeprazole versus rabeprazole with respect to CYP2C19 genotypic differences. Dig Dis Sci 2005;50:1625-31.	3 IM: AA PM: AA	41 patients with peptic ulcers (16x NM, 18x IM, 7x PM) recei-ved omeprazole 20 mg for 8 weeks, approx. 80% Hp-pos, no antacid medication, NSAIDs, anticoagulants or corticoste-roids, co-medication with an effect on CYP2C19 unknown. NM versus IM versus PM: - ulcer size (mm^2) at week 2: 35.8 : 14.6 : 33.9 - ulcer size (mm^2) at week 8: 5.4 : 0.1 : 0.0 - gastric healing ratio (%) at week 2: 63.4 : 85.2 (S) : 84.0 (significance unknown) - gastric healing ratio (%) at week 8: 68.8 : 93.8 : 100 Note: Genotyping was performed for *2 and *3.	

ref. 25 - ulcers/ bleeding Roh HK et al. Omeprazole treatment of Korean patients: effects on gastric pH and gastrin release in relation to CYP2C19 geno- and phenotypes. Basic Clin Pharmacol Toxicol 2004;95:112-9.	3 IM: AA PM: AA	See references on GERD.	
ref. 26 - Hp Zhao F et al. Effect of CYP2C19 genetic polymorphisms on the efficacy of proton pump inhibitor-based triple therapy for Helicobacter pylori eradication: a meta-analysis. Helicobacter 2008;13:532-41.	3 IM: AA# PM: AA #	A meta-analysis of 7 studies with triple therapy (ome + amoxi + clari or ome + amoxi + metro) for 1-2 weeks in Hp-positive patients who had not previously received eradication therapy. Total number of patients and distribution of genotypes was not specified. Only studies with a Jadad quality assessment score ≥ 2 were included. The following two parameters were also considered: randomisation and blindness (double or single blindness either to treatment or genotype groups). However, the results of the quality assessments were not reported. Four of the studies in the meta-analysis were also included in this risk analysis separately (Tanigawara 1999, Dojo 2001, Sapone 2003, and Sheu 2005). 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. Publication bias analysis was not performed. NM versus IM versus PM: - OR for eradication of Hp: 1 : 3.22 (95% CI 1.91-5.42) : 4.28 (95% CI 1.88-9.74)	Authors' conclusion: "The efficacy of omeprazole- and lansoprazole-based first-line triple therapies at the standard doses is dependent on CYP2C19 genotype status."
ref. 27 - Hp Sugimoto M et al. Influences of pro-inflammatory and anti-inflammatory cytokine polymorphisms on eradication rates of clarithromycin-sensitive strains of Helicobacter pylori by triple therapy. Clin Pharmacol Ther 2006;80:41-50.	3 IM: AA# PM: AA #	360 patients (135x NM, 172x IM, 53x PM, clari-susceptible Hp) received 2x daily ome 20 mg (n=90) or lanso 30 mg (n=214) or rabe 10 mg (n=56) + amoxi 750 mg + clari 400 mg for 1 week, co-medication unknown; No association between eradication percentage and PPI type, age, disease and gender. NM versus IM versus PM: - eradication %: 73.3 : 88.4 (S) : 94.3 (S) - OR for eradication failure: 1.0 : 0.439 (S) : 0.251 (S) Note: the IL1B-511 (cytokine) genotype influences the eradication percentage in NM patients. Note: Genotyping was performed for *2 and *3.	
ref. 28 - Hp Gawronska-Szklarz B et al. Effect of CYP2C19 and MDR1 polymorphisms on cure rate in patients with acid-related disorders with Helicobacter pylori infection.	3 IM: AA#	70 patients (56x NM, 14x IM (*1/*2)) received 2x daily ome 20 mg + amoxi 1000 mg + clari 500 mg (n=14) or 2x daily panto 40 mg + amoxi 1000 mg + metro 500 mg (n=56) for 1 week, co-medication unknown; - frequency of NM in group with eradication after treatment is significantly lower than in group without eradication (67.6% versus 91.7%). - frequency of IM in group with eradication is significantly higher than in group without eradication (32.4% versus	

Eur J Clin Pharmacol 2005;61:375-9. **ref. 28, continuation**		8.3%). Note: apart from CYP2C19 genotype, panto/amoxi/metro regimen and genotype for MDR1 also appear to be associated with successful eradication. Note: Genotyping was performed for *2 and *3.	
ref. 29 - 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 2x 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 ome: 68.9 : 84.4 : 91.3, sign trend (int. to treat) 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 metabolizers of CYP2C19."
ref. 30 - Hp Furuta T et al. Polymorphism of interleukin-1beta affects the eradication rates of Helicobacter pylori by triple therapy. Clin Gastroenterol Hepatol 2004;2:22-30.	4 IM: AA# PM: AA#	350 patients (119x NM, 180x IM and 51x PM, 15% clari-resistant Hp) received 2x daily ome 20 mg (n=175) or lanso 30 mg (n=175) + 3x daily amoxi 500 mg + clari 200 mg for 1 week, no co-medication; NM versus IM versus PM: - eradication % of clari-susceptible Hp: 72 : 94 : 98 (S) Note: eradication percentages were not broken down separately for lanso and ome. Note: eradication % for clari-resistant Hp was lower than for non-resistant strains. Note: IL-1β-511 genotype influenced the eradication percentage in NM patients. Note: Genotyping was performed for *2 and *3.	
ref. 31 - Hp Sapone A et al. The clinical role of cytochrome p450 genotypes in Helicobacter pylori management. Am J Gastroenterol 2003;98:1010-5.	3 IM: AA# PM: AA#	143 patients (116x NM, 25x IM and 2x PM (*2/*2)) received 2x daily ome 20 mg + amoxi 1000 mg + clari 500 mg for 1 week, co-medication unknown; NM versus IM versus PM: - phenotype distribution in group with eradication was 75.3% : 22.6% : 2.2% - phenotype distribution in group without eradication was 92% : 8% : 0% - significant association between phenotype NM and eradication failure, OR of univariate analysis is 4.34 (95% CI 1.27-4.82), in multivariate analysis is 3.45 (95% CI 1.11-10.70) Note: Genotyping was performed for *2 and *3.	
ref. 32 - Hp Miwa H et al. Clarithromycin resistance, but not CYP-2C-19 polymorphism, has a major impact on treatment success in 7-day treatment regimen for cure of H. pylori infection: a multiple	3 IM: AA PM: AA	156 patients (of those who could be evaluated, there were 61x NM, 61x IM and 28x PM) received ome 20 mg 2x daily + amoxi 500 mg 3x daily + clari 200 mg 2x daily for 1 week, co-medication unknown; No significant difference in healing percentage between the various genotypes (no figures provided). Note: Genotyping was performed for *2 and *3.	

logistic regression analysis. Dig Dis Sci 2001;46:2445-50.			
ref. 33 - Hp Dojo M et al. Effects of CYP2C19 gene polymorphism on cure rates for Helicobacter pylori infection by triple therapy with proton pump inhibitor (omeprazole or rabeprazole), amoxicillin and clarithromycin in Japan. Dig Liver Dis 2001;33:671-5.	3 IM: AA PM: AA	170 patients (of those who could be evaluated, there were 51x NM, 77x IM and 36x PM) received 2x daily ome 20 mg or rabe 20 mg + amoxi 750 mg + clari 400 mg for 1 week, clari-resistance of Hp unknown, no use of NSAIDs or antibiotics, other co-medication unknown; NM versus IM versus PM: - eradication % with ome: 73.3 : 86.1 (NS) : 85.0 (NS) Note: Genotyping was performed for *2 and *3.	
ref. 34 - Hp Furuta T et al. Effect of genotypic differences in CYP-2C19 on cure rates for Helicobacter pylori infection by triple therapy with a proton pump inhibitor, amoxicillin, and clarithromycin. Clin Pharmacol Ther 2001;69:158-68.	3 IM: AA[#] PM: AA[#]	271 patients (88x NM, 127x IM (95x *1/*2, 32x *1/*3), 46x PM (26x *2/*2, 15x *2/*3, 5x *3/*3)) received 2x daily ome 20 mg (n=136) or lanso 30 mg (n=135) + 3x daily amoxi 500 mg + clari 200 mg for 1 week, PPI was continued for 5-7 weeks, with co-medication: NM versus IM versus PM: - eradication % with ome: 72.7 : 92.1 (S) : 97.8 (S) Note: eradication percentages were not broken down separately for lanso and ome. Note: Genotyping was performed for *2 and *3.	Authors' conclusion: "If the CYP2C19 genotype status is determined before treatment, an optimal dose of a PPI may be prescribable on the basis of this pharmacogenetic or pharmacogenomic status. We also strongly recommend that the doses of PPI's in …H.pylori eradication regimen should be increased,… especially in western countries…"
ref. 35 - Hp Tanigawara Y et al. CYP2C19 genotype-related efficacy of omeprazole for the treatment of infection caused by Helicobacter pylori. Clin Pharmacol Ther 1999;66:528-34.	3 PM: AA[#]	108 patients, 26 patients (10x NM, 12x IM, 4x PM) received duo therapy with ome 20 mg 2x daily + amoxi 500 mg 4x daily, 57 patients (20x NM, 26x IM, 11x PM) received triple therapy with ome 20 mg 2x daily + amoxi 500 mg 4x daily + clari 200 mg 4x daily for 1 week, 25 patients received quadruple therapy without PPI, co-medication unknown. Eradication % NM versus IM versus PM: - duo therapy: 40 : 41 : 100 (NS) - triple therapy: 75 : 88 : 100 (NS) - duo therapy and triple therapy combined: eradication was significantly higher for PM than for (NM + IM) Note: Genotyping was performed for *2 and *3.	Authors' conclusion: "The anti-H pylori effect of dual treatment is highly efficiënt for CYP2C19 poor metabolizers, which suggests that clarithromycin is not necessary as a first line of therapy for this type of patients. Genotyping can provide a choice for the optimal regimen based on individual CYP2C19 genotype."
ref. 36 - Hp Aoyama N et al. Sufficient effect of 1-week omeprazole and amoxicillin dual treatment for Helicobacter pylori eradication in cytochrome P450 2C19 poor metabolizers. J Gastroenterol	3 IM: AA PM: AA	86 patients (of the patients receiving triple therapy there were 35x NM (but this includes 19x IM), 9x PM) received ome 40 mg/day + amoxi 2000 mg/day + clari 800 mg/day for 1 week, no NSAIDs, corticosteroids or antibiotics, other co-medication unknown: NM versus *1/*2 versus *1/*3 versus PM: - eradication %: 81 : 100 (NS) : 75 (NS) : 100 (NS) Note: Genotyping was performed for *2 and *3.	

<table>
<tr><td>1999;34 Suppl 11: 80-3.</td><td></td><td></td><td></td></tr>
<tr><td>ref. 37 – Hp
Inaba T et al.
Helicobacter pylori infection: CYP2C19 genotype and serum ferritin.
J Gastroenterol Hepatol 2002;17:748-53.</td><td>3

IM: AA
PM: AA</td><td>58 patients (21x NM, 27x IM, 10x PM; clarithromycin-susceptible Hp) received 2x daily ome 20 mg + 3x daily amoxi 500 mg + 2x daily clari 200 mg for 1 week, co-medication unknown:

NM versus IM versus PM:
- eradication % with ome: 76.2 : 88.9 (NS) : 90.0 (NS)

Note: Genotyping was performed for *2 and *3.</td><td></td></tr>
<tr><td>ref. 38 - kinetics
Rocha A et al.
Investigation of the in vivo activity of CYP3A in Brazilian volunteers: comparison of midazolam and omeprazole as drug markers.
Eur J Clin Pharmacol 2008;64:901-6.</td><td>3

UM: AA
*17: AA</td><td>9 healthy volunteers (3x *1/*1, 3x *1/*17, 2x *17/*17, 1x *2/*17) received a single dose of 20 mg omeprazole after 12 hours of fasting. Co-medication, interacting foods and smoking were excluded. Plasma concentrations were determined 3.5 hours after administration.

MR omeprazole/hydroxyomeprazole (mean (range)):
*1/*1: 1.73 (0.93-3.02)
*1/*17: 1.18 (0.28-1.91)
*17/*17: 0.99 (0.20-1.78)
*2/*17: 3.55
The significance of the differences was not determined. According to the authors, all the volunteers were NM (MR <4.0), but this MR was determined in volunteers with *1/*1, *1/*17 or *17/*17.

Note: Genotyping was performed for *2, *3 and *17.</td><td></td></tr>
<tr><td>ref. 39 - kinetics
Baldwin RM et al.
Increased omeprazole metabolism in carriers of the CYP2C19*17 allele; a pharmacokinetic study in healthy volunteers.
Br J Clin Pharmacol 2008;65:767-74.</td><td>3

UM: A</td><td>16 healthy volunteers (11x *1/*1, 5x *17/*17) received a single dose of 40 mg omeprazole. Co-medication and interacting foods were excluded. Plasma concentrations were determined up to 10 hours after administration.

*17/*17 versus *1/*1:
- decrease in AUC by 52% (S; from 4,151 to 1,973 h.nmol/L).
- decrease in the metabolic ratio AUC omeprazole/ 5-hydroxyomeprazole by 45% (S; from 1.2 to 0.66).
- lower inter-individual variation in the metabolic ratio (reduction in width of 95% confidence interval by 72% from 0.70-1.60 to 0.54-0.79).
- non-significant reduction in $t_{1/2}$ of omeprazole.

Note: Genotyping was performed for *2 and *17.</td><td>Authors' conclusion: "For clinically important drugs that are metabolized predominantly by CYP-2C19, the CYP2C19 *17 allele might be associated with subtherapeutic drug exposure."</td></tr>
<tr><td>ref. 40 - kinetics
Hu XP et al.
Effects of CYP2C19 genetic polymorphism on the pharmacokinetics and pharmacodynamics of omeprazole in Chinese people.
J Clin Pharm Ther 2007;32:517-24.
PubMed PMID: 17875119.</td><td>4

PM: A
IM: AA</td><td>18 healthy volunteers, selected on basis of their CYP2C19 genotype, received omeprazole 20 mg once daily for 8 days. Co-medication, excessive alcohol consumption and excessive smoking were excluded.

Genotyping:
- 6x NM
- 6x IM
- 6x PM

Results:
<table>
<tr><td colspan="4">AUC_{0-24h} compared to NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>value for NM</td></tr>
<tr><td>day 8</td><td>x 3.28 (S)</td><td>x 1.25 (NS)</td><td>2.42 µg.h/ml</td></tr>
<tr><td>day 1</td><td>x 4.15 (S)</td><td>x 1.07 (NS)</td><td>1.64 µg.h/ml</td></tr>
<tr><td colspan="4">For NM and IM, but not for PM, the AUC at day 8 was significantly higher than the AUC at day 1. These data show that the increase with multiple dosing is due to inhi-</td></tr>
</table></td><td>Authors' conclusion: 'The pharmacodynamic effects of omeprazole and its pharmacokinetics depend on the CYP2C19 genotype status in Chinese people.'

AUC versus NM:
IM: 125%
PM: 328%</td></tr>
</table>

ref. 40, continuation		bition of CYP2C19. Note: Genotyping was for *2 and *3. These are the most important gene variants in this Chinese population.	
ref 41 - kinetics Sim SC et al. A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. Clin Pharmacol Ther 2006;79:103-13.	3 UM: A *17: A	107 healthy volunteers (71x *1/*1, 32x *1/*17, 4x *17/*17) received a single dose of 20 mg omeprazole. Metabolic ratios were determined based on the plasma concentrations 3 hours after administration. *17/*17 versus *1/*1: - decrease in the median metabolic ratio omeprazole/ 5-hydroxyomeprazole by 50% (S; from 0.500 to 0.250). - decrease in the predicted AUC based on the correlation between AUC and MR in 24 individuals by 37% (from 1,171 to 742 h.nmol/L). *1/*17 versus *1/*1: - decrease in the median metabolic ratio omeprazole/ 5-hydroxyomeprazole by 19% (S; from 0.500 to 0.405). - decrease in the predicted AUC based on the correlation between AUC and MR in 24 individuals by 14% (from 1,171 to 1,010 h.nmol/L).	Authors' conclusion: "CYP2C19*17 is likely to cause therapeutic failures in drug treatment with, for example, proton pump inhibitors and antidepressants. …. On the basis of our genotype-phenotype data on carriers of the CYP2C19*17 allele, it would be beneficial to subdivide the homozygous NM group into 3 groups based on the number of CYP2C19 *17 alleles that the subjects carry."
ref. 42 SmPC Losec (omeprazole) 30-08-23.	0 PM: A	In CYP2C19 poor metabolisers, omeprazole is probably primarily metabolised by CYP3A4. After repeated once daily dosing of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in those with a functioning CYP2C19 enzyme (normal metabolisers). Mean peak plasma concentrations were also increased (3 to 5 times). These findings do not impact the omeprazole dose.	AUC versus (NM + IM): PM: 500-1000%
ref. 43 SmPC Prilosec (omeprazole), USA, 18-07-23.	0 PM: A IM: A	<u>Pharmacogenomics</u>: In normal metabolizers, omeprazole is primarily metabolized by CYP2C19. The systemic exposure to omeprazole varies with a patient's metabolism status: poor metabolizers > intermediate metabolizers > normal metabolizers. <u>Drug interactions</u>: Clinically relevant interactions affecting drugs co-administered with omeprazole: Tacrolimus. Clinical impact: potential for increased exposure of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.	

[#] In these cases, there was a significant difference between NM and IM or PM, but the clinical effect was more favourable for IM or PM than for NM. As the classification of the severity of the effect aims to classify negative effects, the code AA is used for a positive effect.

Risk group	UM with inducers of CYP2C19 and/or CYP3A4

Comments:

- Of the articles on efficiency of not-genotype-guided therapy published after 2009, only articles were included with data on subjects with the *17-variant or with data on ulcers/bleeding from more than 25 subjects, on gastroesophageal reflux disease from more than 50 subjects or on Helicobacter pylori from more than 200 subjects. For IM and PM, only kinetic studies were included with oral administration, repeated doses, at least 1 PM and data on AUC, steady state concentration or clearance in comparison with NMs. After 2009, the same criteria were applied for inclusion of kinetic studies with patients with the *17-variant, except for the requirement of at least 1 patient with a *17-variant instead of at least 1 PM.
  Other studies did not add enough to the evidence to be included.
  Studies with a discrepancy between phenotyping and genotyping data were not included.
  Studies with eradication therapy based on two or four medicines were not included in the risk analysis, nor studies in which the dose of the PPI was lower than the dose registered for eradication in the Netherlands.
  The study of Cicali et al. comparing genotype-guided and not-genotype guided therapy (Cicali EJ er al. Novel implementation of genotype-guided proton pump inhibitor medication therapy in children: a pilot, randomized, multisite

pragmatic trial. Clin Transl Sci 2019;12:172-9. PMID: 30341969) was not included in the risk analysis, because 15% of the patients in this study used another PPI than omeprazole. In addition, 6.7% of the patients in this study used esomeprazole for which no clinical effect of CYP2C19 genotype has been observed. Finally, the PPI dose was halved for IM and PM in this study, while convincing evidence for a negative clinical effect in IM and PM using omeprazole is lacking.

- 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 Medicine Information Centre: 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/dosing recommendations**:
  - 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'. However, CPIC dosing recommendations for PPIs do not differ between *1/*17 and *1/*1, between IM and 'likely IM' and between PM and 'likely PM'. The summary below uses the KNMP definitions for NM, PM, IM and UM.
    CPIC indicates that there is a substantial body of evidence linking CYP2C19 genotype with variability in plasma concentrations and efficacy of first-generation PPIs, like omeprazole. CPIC states that the evidence associating CYP2C19 genotype with omeprazole plasma concentrations was graded as high (i.e. evidence includes consistent results from well-designed, well-conducted studies). CPIC indicates that multiple studies have shown that the CYP2C19 IM and PM phenotypes are associated with decreased clearance and increased plasma concentrations of first generation PPIs leading to increased treatment success compared with CYP2C19 NM, including for H. pylori infection and erosive esophagitis *(*Furuta T et al. Effect of genetic differences in omeprazole metabolism on cure rates for Helicobacter pylori infection and peptic ulcer. Ann Intern Med 1998;129:1027-30, Ichikawa H et al. Rapid metabolizer genotype of CYP2C19 is a risk factor of being refractory to proton pump inhibitor therapy for reflux esophagitis. J Gastroenterol Hepatol 2016;31:716-26, and Lin YA et al. Effect of CYP2C19 gene polymorphisms on proton pump inhibitor, amoxicillin, and levofloxacin triple therapy for eradication of Helicobacter Pylori. Med Sci Monit 2017;23:2701-7). CPIC states that, in contrast, CYP2C19 *1/*17 and UM have increased PPI clearance and decreased plasma concentrations compared with CYP2C19 *1/*1, which may increase risk of treatment failure compared with CYP2C19 *1/*1, IM, and PM (Sim 2006 and Gawrońska-Szklarz B et al. CYP2C19 polymorphism affects single-dose pharmacokinetics of oral pantoprazole in healthy volunteers. Eur J Clin Pharmacol 2012; 68:1267-74). CPIC indicates that it is important to note that most CYP2C19 studies evaluating PPIs were conducted in Asian populations, in whom the frequency of the increased function CYP2C19*17 allele is low compared with non-Asians; therefore, few studies including CYP2C19 *1/*17 and UM have been published to date. CPIC indicates that prescribing recommendations for CYP2C19 *1/*17 and UM in the CPIC guideline were based on pharmacokinetic differences versus *1/*1 and differences in PPI effectiveness between *1/*1 and IM/PM.
    CPIC indicates that the therapeutic recommendations for PPI prescribing apply to both adults and paediatric

patients and to both oral and intravenous PPI use. CPIC states that, while CYP2C19 *1/*1 are expected to have normal PPI metabolism and clearance, a large body of literature from studies in Asian populations reported an association between CYP2C19 *1/*1 and decreased therapeutic effectiveness with first generation PPIs (e.g., failure to eradicate H. pylori infection and lower healing rates of erosive esophagitis) compared with CYP2C19 IM and PM. CPIC indicates, that therefore, for CYP2C19 *1/*1, initiating these PPIs at standard daily doses (e.g., label-recommended doses) is generally recommended; however, for H. pylori infection or erosive esophagitis, clinicians may consider increasing the recommended dose for these indications by 50-100% to optimize therapeutic efficacy.

CPIC indicates that, following administration of standard doses of first-generation PPIs, CYP2C19 IM and PM experience higher PPI AUC (3-14-fold) and maximum plasma drug concentration (2-6-fold) compared with CYP2C19 *1/*1 as a result of reduced PPI clearance via the CYP2C19 pathway (Chang M et al. Interphenotype differences in disposition and effect on gastrin levels of omeprazole–suitability of omeprazole as a probe for CYP2C19. Br J Clin Pharmacol 1995;39:511-8, Tanaka M et al. Stereoselective pharmacokinetics of pantoprazole, a proton pump inhibitor, in extensive and poor metabolizers of S-mephenytoin. Clin Pharmacol Ther 2001;69:108-13, Kim K-A et al. Enantioselective disposition of lansoprazole in extensive and poor metabolizers of CYP2C19. Clin Pharmacol Ther 2002;72:90-9, and He N et al. Inhibitory effect of troleandomycin on the metabolism of omeprazole is CYP2C19 genotype-dependent. Xenobiotica 2003;33:211-21). CPIC indicates that the increased PPI exposure in CYP2C19 IM and PM has been linked to improved acid suppression (i.e., higher intragastric pH and longer time with pH > 4.0) and improved therapeutic benefits. CPIC states, that. thus, CYP2C19 IM and PM are considered to be “therapeutically advantaged” compared with *1/*1 in terms of efficacy (Furuta 1999, Shimatani 2003, Park 2017, Chen W-Y et al. Double-dosed pantoprazole accelerates the sustained symptomatic response in overweight and obese patients with reflux esophagitis in Los Angeles grades A and B. Am J Gastroenterol 2010;105:1046-52, and Kurzawski M et al. Effect of CYP2C19*17 gene variant on Helicobacter pylori eradication in peptic ulcer patients. Eur J Clin Pharmacol 2006;62:877-80). CPIC indicates that, however, it has been suggested that continued inhibition of acid secretion in individuals taking PPIs chronically who are genotyped as CYP2C19 IM or PM may have a higher risk of PPI-related adverse events compared with NM or UM phenotypes (El Rouby N et al. Proton pump inhibitors: from CYP2C19 pharmacogenetics to precision medicine. Expert Opin Drug Metab Toxicol 2018;14:447-60). CPIC states that, while the current data are insufficient to make strong dosing recommendations, potential associations of CYP2C19 phenotype and incidence of adverse events (e.g., infections) are emerging (Bernal CJ et al. CYP2C19 phenotype and risk of proton pump inhibitor-associated infections. Pediatrics 2019;144: e20190857). CPIC indicates, that, therefore, for CYP2C19 IM and PM, it is recommended to initiate standard daily dosing to maximize the likelihood of efficacy and, once efficacy is achieved, consider a 50% reduction in the daily dose in the setting of chronic PPI therapy (beyond 12 weeks) to minimize the risk of adverse events from prolonged acid suppression. CPIC indicates, that if a dose reduction is made, monitoring for continued efficacy is recommended. In addition, CPIC indicates that additional studies that investigate the relationship between CYP2C19 genotype and incidence of PPI-related adverse events are needed.

CPIC indicates that the phenotypes of *1/*17 and UM are driven by the presence of the increased function CYP2C19*17 allele. CPIC states, that due to the relatively recent discovery of this variant (Sim 2006) and because the majority of studies describing associations between CYP2C19 genotype, pharmacokinetics, and pharmacodynamics of PPIs were conducted in Asian populations in whom the CYP2C19*17 allele occurs less frequently, there are limited data on the relationship between CYP2C19*17, pharmacokinetic parameters, acid secretion indices, and therapeutic outcomes in CYP2C19 *1/*17 and UM. CPIC states that additional studies with CYP2C19 *1/*17 and UM are needed. CPIC indicates that, nevertheless, the low PPI exposure documented in patients who are CYP2C19 UM compared with *1/*1, IM, and PM suggests that these individuals may benefit from higher-than-standard daily doses of PPIs. CPIC indicates, that, therefore, it is recommended to increase the starting daily dose by 100% in CYP2C19 UM. For *1/*17, CPIC gives the same therapeutic recommendation as for *1/*1.

CPIC indicates that the plasma half-life of PPIs is short (~ 30 minutes to 5 hours), but the biological effects they exert are much longer, as it takes ~ 54 hours to regenerate new acid pumps after inactivation by PPIs. CPIC indicates, that studies have documented that daily doses administered two to four times daily may result in improved efficacy compared with the same total daily dose given once daily (Furuta T et al. Pharmacogenomics-based tailored versus standard therapeutic regimen for eradication of H. pylori. Clin Pharmacol Ther 2007;81:521-8 and Ormeci A et al. Can Helicobacter pylori be eradicated with high-dose proton pump inhibitor in extensive metabolizers with the CYP2C19 genotypic polymorphism? Eur Rev Med Pharmacol Sci 2016;20:1795-7). CPIC indicates that, although adherence to PPI dosing three to four times per day to overcome the short half-life may be challenging, it is recommended that increased PPI doses (50–100%) be administered as twice daily dosing, and more frequent dosing intervals could be considered for increased benefit, with the caveat that this dosing regimen may compromise compliance.

Dosing recommendations for omeprazole based on CYP2C19 phenotype		
Phenotype	Therapeutic recommendation	Classification of recommendation
UM	Increase starting daily dose by 100%. Daily dose may be given in divided doses. Monitor for efficacy.	Optional[a]
NM	Initiate standard starting daily dose. Consider increasing dose by 50–100% for the treatment of	Moderate[b]

	H. pylori infection and erosive esophagitis. Daily dose may be given in divided doses. Monitor for efficacy.	
IM	Initiate standard starting daily dose. For chronic therapy (> 12 weeks) and efficacy achieved, consider 50% reduction in daily dose and moni-tor for continued efficacy	Optional[a]
PM	Initiate standard starting daily dose. For chronic therapy (> 12 weeks) and efficacy achieved, consider 50% reduction in daily dose and moni-tor for continued efficacy	Moderate[b]

[a] The classification optional indicates that the desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.

[b] The classification moderate indicates that there is a close or uncertain balance as to whether the evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

With regard to paediatrics, CPIC indicates that In children older than one year of age, there is emerging evidence that CYP2C19 genetic variation influences PPI pharmacokinetics and response (Bernal CJ et al. CYP2C19 phenotype and risk of proton pump inhibitor-associated infections. Pediatrics 2019;144:e20190857, Knebel W et al. Population pharmacokinetic modeling of pantoprazole in pediatric patients from birth to 16 years. J Clin Pharmacol 2011;51:333-45, Shakhnovich V et al. A population-based pharmacokinetic model approach to pantoprazole dosing for obese children and adolescents. Paediatr Drugs 2018;20:483-95, and Kearns GL et al. Single-dose pharmacokinetics of oral and intravenous pantoprazole in children and adolescents. J Clin Pharmacol 2008;48: 1356-65). CPIC indicates that CYP2C19 *1/*17 and UM have been associated with decreased efficacy compared with PM and *1/*1 when treating paediatric GERD and eosinophilic esophagitis (Franciosi JP et al. Association between CYP2C19*17 alleles and pH probe testing outcomes in children with symptomatic gastroesophageal reflux. J Clin Pharmacol 2018;58:89-96, Franciosi JP et al. Association between CYP2C19 extensive metabolizer phenotype and childhood anti-reflux surgery following failed proton pump inhibitor medication treatment. Eur J Pediatr 2018;177:69-77, and Mougey EB et al. CYP2C19 and STAT6 variants influence the outcome of proton pump inhibitor therapy in pediatric eosinophilic esophagitis. J Pediatr Gastroenterol Nutr 2019;69:581-7). CPIC indicates that the CYP2C19 PM phenotype is associated with higher rates of respiratory and gastrointestinal infections than *1/*1, *1/*17, or UM (Lima JJ et al. Association of CYP2C19 polymorphisms and lansoprazole-associated respiratory adverse effects in children. J Pediatr 2013;163:686-91). In addition, CPIC indicates that a recent pilot study of CYP2C19-genotype-guided dosing of PPIs in children has been promising, and additional studies are ongoing (Cicali EJ et al. Novel implementation of genotype-guided proton pump inhibitor medication therapy in children: a pilot, randomized, multisite pragmatic trial. Clin Transl Sci 2019;12:172-9 and Tang M et al. Genotype tailored treatment of mild symptomatic acid reflux in children with uncontrolled asthma (GenARA): Rationale and methods. Contemp Clin Trials 2019;78:27-33). CPIC states that these reports support genotype-based optimization of PPI therapy for children. CPIC indicates that, however, very low clearance in preterm infants and infants less than 2–3 months of age (Knebel W et al. Population pharmacokinetic modeling of pantoprazole in pediatric patients from birth to 16 years. J Clin Pharmacol 2011;51:333-45) makes recommendations in the neonatal population difficult to support.

On 22-7-2024, there was not a more recent version of the recommendations present on the CPIC-site.

- Kita T et al. Optimal dose of omeprazole for CYP2C19 extensive metabolizers in anti-Helicobacter pylori therapy: pharmacokinetic considerations. Biol Pharm Bull 2002;25:923-7. PubMed PMID: 12132671.

  Based on a pharmacokinetic study with single doses of omeprazole 20 mg, 40 mg and 80 mg for 3 PM and 4 NM, the authors recommend a maximum dose of omeprazole 80 mg twice daily for eradication of H. pylori in NMs. The AUC of omeprazole in PM after a single 20 mg dose was almost equal to the AUC in NM after a single 80 mg dose.

  Co-medication was excluded.

  The AUC ratio of PM versus NM was 15, 14 and 3.6 at doses of respectively 20, 40 and 80 mg.

  The AUC increase in NM when the dose was doubled was 3.2-fold for the increase from 20 to 40 mg and 6.0-fold for the increase from 40 to 80 mg, indicating non-linear pharmacokinetics. The data for PM were respectively 3.0-fold and 1.5-fold, with the mean of 2.2-fold suggesting linear pharmacokinetics. Thus, the non-linear pharmacokinetics for NM is most probably due to saturation of the metabolic capacity of CYP2C19.

  Note: the authors did not take into account, that the AUC-ratio between PM and NM is different after single and multiple dosing due to the inhibition of CYP2C19 by omeprazole.

Date of literature search: 1 July 2024.

	Phenotype	**Code**	**Gene-drug interaction**	**Action**	**Date**
KNMP Pharmacogenetics Working Group decision	PM	4 AA[#]	yes	no	10 September 2024
	IM	4 AA[#]	yes	no	
	UM	3 E	yes	yes	

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

Mechanism:
Omeprazole is primarily converted by CYP2C19 to the inactive hydroxy metabolite. In addition to this, omeprazole is converted by CYP3A4 to omeprazole sulfone. Omeprazole is an inhibitor of CYP2C19 and thereby of its own metabolism. This results in non-linear pharmacokinetics. With doses higher than 40 mg a greater than linear response in AUC occurs.
Reduced CYP2C19 activity results in higher plasma concentrations and a higher omeprazole AUC and can therefore result in improved therapeutic effectiveness and/or a higher incidence of side effects. The extent and duration of effective acid inhibition by proton pump inhibitors is dependent on the AUC.

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 available, the DPWG recommends adhering to the gene-drug guideline	0-2 +
Beneficial	PGx testing for this gene-drug pair is beneficial. It is advised to consider genotyping 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+	2+
Corresponding Clinical Implication Score:		Potentially beneficial