CYP2C19: omeprazole 1839 to 1841

amoxi = amoxicillin, AUC = area under the concentration-time curve, CI = confidence interval, clari = clarithromycin, Cl_{or} = oral clearance, EM = extensive metaboliser (*1/*1, *1/*17) (normal CYP2C19 enzyme activity), 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, 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, UM = ultra-rapid metaboliser (*17/*17) (increased CYP2C19 enzyme activity).

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

Brief summary and justification of choices:

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 thus 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 both meta-analyses and 6 of the 10 studies for both PM and IM), reflux oesophagitis (significant in 3 of the 7 studies for PM and 5 of the 9 studies for IM) and peptic ulcer/bleeding (significant in 1 of the 6 studies for PM and 2 of the 5 studies for IM) suggested that the dose in EM patients is actually suboptimal. An increase in side effects was not observed for IM and PM.

Because of the observed kinetic effect, the working group concludes 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 there are no studies into the clinical consequences. However, decreased therapeutic effectiveness on eradication of Helicobacter pylori and reflux oesophagitis was found for EM 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 working group concludes that there is a gene-drug interaction. The working group concludes that there is not enough evidence that this results in an effect of UM or *17 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 EM 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 EM+IM after repeated dosing, which was much higher than the difference observed between PM and EM 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 EM, the dose of S-omeprazole is 4-fold higher than for omeprazole (due to the recommended dose being 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 working group considers it to be save and most appropiate to recommend the

median calculated dose increase of 328% instead of the mean calculated dose increase of 178%. The Dutch 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 on 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 Dutch 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 Dutch Pharmacogenetics Working Group recommends adhering to the gene-drug guideline.
The clinical implication of the gene-drug interaction scores 0 out of the maximum of 10 points (with pre-emptive genotyping considered to be potentially beneficial for scores ranging from 0 to 2 points):
Omeprazole showed diminished efficacy in patients without genetically diminished CYP2C19 activity (extensive or normal metabolisers (EM) and ultra-rapid metabolisers (UM)). However, diminished efficacy has not been substantiated for UM compared to EM. In addition, this diminished efficacy does not have a high clinical impact (severity code B or C corresponding to CTCAE grade 1 or 2). This results in a score of 0 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 (only points for CTCAE grade ≥ 3).
The lack of a severe clinical effect also results in a score of 0 of the maximum of 3 points for the second and third criterion of the clinical implication score: the level of evidence supporting an associated clinical effect grade ≥ 3 and the number needed to genotype (NNG) in the Dutch population to prevent one clinical effect code ≥ D (grade ≥ 3).
The Summary of Product Characteristics (SmPC) does not mention the CYP2C19 UM phenotype. This results in 0 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (only points for the phenotype at least being mentioned in the SmPC).

The table below follows the KNMP definitions for EM, PM, IM and UM. The definitions of EM, 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: EM : IM (S or NS versus EM) : PM (S or NS versus EM).

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.

<table>
<tr><th>Source</th><th>Code</th><th>Effect</th><th>Comments</th></tr>
<tr><td>ref. 1 - 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 EM
- 6x IM
- 8x PM

Results:
<table>
<tr><td colspan="4">$AUC_{0\text{-}12h}$ compared to EM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>value for EM</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 CYP2C19*2 and *3 influence the pharmacokinetics and pharmacodynamics of omeprazole in Korean healthy volunteers.'

AUC versus EM:
IM: 122%
PM: 214%</td></tr>
<tr><td>ref. 2 - ulcers/bleeding
Chwiesko A et al.
Effects of different omeprazole dosing on gastric pH in</td><td>3</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</td><td>Authors' conclusion: 'In both groups, CYP2C19 genotypes (*1/*1, *1/*17, *17/*17) had no essential effect on</td></tr>
</table>

<table>
<tr>
<td>non-variceal upper gastrointestinal bleeding: a randomized prospective study.
J Dig Dis 2016;17:588-599.
PubMed PMID: 27518195.

ref. 2, continuation</td>
<td>

*17: AA</td>
<td>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_{0-6hr} for each dosing regimen</td><td>NS</td></tr>
</table>

Note: Genotyping was for *2, *3 and *17.</td>
<td>intragastric pH.'</td>
</tr>
<tr>
<td>ref. 3 - 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>4

PM: AA#
IM: AA#</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.
Three of the trials in the meta-analysis were also included in 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.

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

Results:
<table>
<tr><td colspan="2">H. pylori eradication rate compared to EM (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 EM, suggests that EMs may need to take a higher-than-standard dose of omeprazole.</td>
<td>Authors' conclusion:
'Carriage of CYP2C19 loss-of-function variants is associated with increased H. pylori eradication rate in patients taking PPI-based triple therapies when omeprazole or lansoprazole is chosen.'</td>
</tr>
<tr>
<td>ref. 4 - GERD
Dury S et al.
Agranulocytosis induced by proton pump inhibitors.
J Clin Gastroenterol 2012;46:859.
PubMed PMID: 22240865.</td>
<td>2</td>
<td>A 20-year-old man with cystic fibrosis developed septic shock due to agranulocytosis (white blood cells 0.7×10^9/L; neutrophils < 0.1×10^9/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.</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>
</table>

<table>
<tr><td>ref. 4, continuation</td><td>UM: E</td><td>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></td></tr>
<tr><td>ref. 5 - 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

PM: AA
IM: AA</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 EM
- 67x IM
- 38x PM

Results:
<table><tr><td colspan="3">Percentage of patients with ulcer complete healing for PM versus IM versus EM:</td></tr><tr><td></td><td></td><td>value for EM</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>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>
<tr><td>ref. 6 - 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 EM
- 23x IM

Results:
<table><tr><td colspan="3">Results compared to EM:</td></tr><tr><td></td><td>IM</td><td>value for EM</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. 7 - GERD
Helsby NA et al. Omeprazole-induced acute interstitial nephritis is not rela-</td><td>3</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.</td><td>Authors’ conclusion: ‘The CYP2C19 poor metabolizer genotype was not over represented in</td></tr>
</table>

ted to CYP2C19 genotype or CYP-2C19 phenotype. Br J Clin Pharmacol 2010;69:516-9. PubMed PMID: 20573087. **ref. 7, continuation**	IM: AA PM: AA	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 EM - 5x IM Results: Genotype distribution of patients with acute interstitial nephritis compared with that of a reference population: NS Note: Genotyping was for *2 and *3. Next to *17, these are the most important gene variants in this New-Zealand population.	patients with omeprazole-induced acute interstitial nephritis.'
ref. 8 - GERD Saitoh T et al. Influences of CYP-2C19 polymorphism on recurrence of reflux esophagitis during proton pump inhibitor maintenance therapy. Hepatogastroenterology 2009;56:703-6.	3 IM: AA PM: AA	28 patients whose GERD had healed after omeprazole 20 mg/day for 8 weeks (8x EM, 14x IM, 6x PM, 39% Hp-pos) received omeprazole 20 mg/day as maintenance therapy for 6 months, co-medication unknown; EM versus IM versus PM: - frequency of recurrence of GERD symptoms (%): 50 : 14 (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 EM. Note: Genotyping was performed for *2 and *3.	
ref 9 - 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 EM: PM: 428% IM: 317%
ref. 10 - GERD Ohkusa T et al. Effect of CYP2C19 polymorphism on the safety and effi-	3	119 patients with reflux oesophagitis grade A-D (46x EM, 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;	Authors' conclusion: "These data clearly indicate that genotype determination of the purpose of

cacy of omeprazole in Japanese patients with recurrent reflux esophagitis. Aliment Pharmacol Ther 2005;21:1331-9.	IM: AA PM: AA	EM 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.	dose adjustment is not necessary in Japanese patients undergoing long-term therapy with 1-10 mg of 20 mg omeprazole daily."
ref. 11 - 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 EM, 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; EM 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 EM: IM: 97% PM: 101%
ref. 12 - GERD Shirai N et al. Effects of CYP2C19 genotypic differences in the metabolism of omeprazole and rabeprazole on intragastric pH. Aliment Pharmacol Ther 2001;15:1929-37.	4 IM: AA[#] PM: AA[#]	15 healthy volunteers (6x EM, 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; EM versus IM versus PM: - 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 EM: IM: 229% PM: 677%
ref. 13 - 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 EM 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: EM 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. 14 - 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 EM, 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: EM 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. 15 - 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-
	4
	
	IM: AA
	PM: AA[#]
		18 healthy men (6x EM, 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.
		
		EM 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:
			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."

receptor antagonist. Aliment Pharmacol Ther 2003;18:1149-1157.		- 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.	
ref. 16 - 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 EM, 14x IM, 6x PM) received omeprazole 20 mg 1x daily for 8 weeks, 89% Hp-pos, no antacid medication, NSAIDs, anticoagulants, corticosteroids or gastrokinetics, co-medication with an effect on CYP-2C19 unknown. EM 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 EM patients. Similarly, the improvement ratio in PM patients was apparently greater than that in EM patients although the difference was not statistically significant."
ref. 17 - ulcers/ bleeding Sugimoto M et al. Initial 48-hour acid inhibition by intravenous infusion of omeprazole, famotidine, or both in relation to cytochrome P450 2C19 genotype status. Clin Pharmacol Ther 2006;80:539-48.	4 IM: AA[#] PM: AA [#]	15 Hp-positive volunteers (5x EM, 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; EM 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, EM 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 EM 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, EM 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.	Authors' conclusion: "This study suggests that the CYP2C19 genotyping test appears to be a useful tool for determining 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 EMs and concomitant infusion of 20 mg omeprazole plus 20 mg famotidine twice daily in homozygous EMs of CYP2C19."
ref. 18 - ulcers/ bleeding Ji S et al.	3	53 patients with active peptic ulcers (3x EM, 25x IM, 25x PM) received omeprazole 20 mg 1x daily for 6 weeks, 77% Hp-pos, no antacid medication, anticoagulants, corticoste-	Authors' conclusion: "CYP2C19 genotypes had no effect

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.	PM: AA	roids, anticholinergics, antidepressants or oncolytics, co-medication with an effect on CYP2C19 unknown. (EM + 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 EM + IM group consisted primarily of IM Note: Genotyping was performed for *2 and *3.	on the remaining ratio of peptic ulcers after 1 week and the healing rate of peptic ulcers after 6 weeks."
ref. 19 - 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 EM, 18x IM, 7x PM) received omeprazole 20 mg for 8 weeks, approx. 80% Hp-pos, no antacid medication, NSAIDs, anticoagulants or corticosteroids, co-medication with an effect on CYP2C19 unknown. EM 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. 20 - 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. 21 - 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 11 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. EM 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. 22 - 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 EM, 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. EM 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 EM patients.	

		Note: Genotyping was performed for *2 and *3.	
ref. 23 - 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. Eur J Clin Pharmacol 2005;61:375-9.	3 IM: AA#	70 patients (56x EM, 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 EM 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 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. 24 - 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 EM, 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; EM versus IM versus PM: - Eradication % with ome: 68.9 : 84.4 : 91.3, sign trend (int. to treat) In EM 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 homologous extensive metabolizers of CYP2C19."
ref. 25 - 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 EM, 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; EM 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 EM patients. Note: Genotyping was performed for *2 and *3.	
ref. 26 - 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 EM, 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; EM 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 EM 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. 27 - 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 logistic regression analysis. Dig Dis Sci 2001;46:2445-50.	3 IM: AA PM: AA	156 patients (of those who could be evaluated, there were 61x EM, 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.	
ref. 28 - 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 EM, 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; EM versus IM versus PM: eradication % with ome: 73.3 : 86.1 (NS) : 85.0 (NS) Note: Genotyping was performed for *2 and *3.	
ref. 29 - 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 EM, 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: EM 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. 30 - 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 EM, 12x IM, 4x PM) received duo therapy with ome 20 mg 2x daily + amoxi 500 mg 4x daily, 57 patients (20x EM, 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 % EM 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 and for (EM + 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

ref. 30, continuation			CYP2C19 genotype.”
ref. 31 - 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 1999;34 Suppl 11: 80-3.	3 IM: AA PM: AA	86 patients (of the patients receiving triple therapy there were 35x EM (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: EM versus *1/*2 versus *1/*3 versus PM: - eradication %: 81 : 100 (NS) : 75 (NS) : 100 (NS) Note: Genotyping was performed for *2 and *3.	
ref. 32 – Hp Inaba T et al. Helicobacter pylori infection: CYP2C19 genotype and serum ferritin. J Gastroenterol Hepatol 2002;17:748-53.	3 IM: AA PM: AA	58 patients (21x EM, 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: EM versus IM versus PM: - eradication % with ome: 76.2 : 88.9 (NS) : 90.0 (NS) Note: Genotyping was performed for *2 and *3.	
ref. 33 - 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.	3 UM: AA *17: AA	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 EM (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.	
ref. 34 - 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.	3 UM: A	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.	Authors’ conclusion: “For clinically important drugs that are metabolized predominantly by CYP-2C19, the CYP2C19 *17 allele might be associated with subtherapeutic drug exposure.”
ref. 35 - kinetics Hu XP et al. Effects of CYP2C19 genetic polymorphism on the pharmacokinetics and	4	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:	Authors’ conclusion: ‘The pharmacodynamic effects of omeprazole and its pharmacokinetics depend on the

<table>
<tr>
<td>pharmacodynamics of omeprazole in Chinese people.
J Clin Pharm Ther 2007;32:517-24.
PubMed PMID: 17875119.

ref. 35, continuation</td>
<td>PM: A
IM: AA</td>
<td>- 6x EM
- 6x IM
- 6x PM

Results:
<table>
<tr><td colspan="4">AUC_{0-24h} compared to EM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>value for EM</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 EM 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 inhibition of CYP2C19.</td></tr>
</table>

Note: Genotyping was for *2 and *3. These are the most important gene variants in this Chinese population.</td>
<td>CYP2C19 genotype status in Chinese people.’

AUC versus EM:
IM: 125%
PM: 328%</td>
</tr>
<tr>
<td>ref 36 - 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.</td>
<td>3

UM: A

*17: A</td>
<td>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).</td>
<td>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 EM group into 3 groups based on the number of CYP2C19 *17 alleles that the subjects carry.”</td>
</tr>
<tr>
<td>ref. 37
SmPC Losec (omeprazole) 14-01-17.</td>
<td>0

PM: A</td>
<td>After repeated once daily dosing of 20 mg omeprazole, the mean AUC was approximately 5 to 10 times higher in poor metabolisers than in those with a functioning CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also increased (3 to 5 times). These findings do not impact the omeprazole dose.</td>
<td>AUC versus (EM + IM):
PM: 500-1000%</td>
</tr>
<tr>
<td>ref. 38
SmPC Prilosec (omeprazole), USA, 19-12-16.</td>
<td>0

PM: A
IM: A</td>
<td>In extensive metabolizers, omeprazole is primarily metabolized by CYP2C19. The systemic exposure to omeprazole varies with a patient’s metabolism status: poor metabolizers > intermediate metabolizers > extensive metabolizers.</td>
<td></td>
</tr>
</table>

[#] In these cases, there was a significant difference between EM and IM or PM, but the clinical effect was more favourable for IM or PM than for EM. 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 efficacy 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 EMs. 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 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 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 EM 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 EM : 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 heterozygote extensive 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 dosing recommendations
  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 EM, the authors recommend a maximum dose of omeprazole 80 mg twice daily for eradication of H. pylori in EMs. The AUC of omeprazole in PM after a single 20 mg dose was almost equal to the AUC in EM after a single 80 mg dose. Co-medication was excluded.
  The AUC ratio of PM versus EM was 15, 14 and 3.6 at doses of respectively 20, 40 and 80 mg.
  The AUC increase in EM 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 EM 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 EM is different after single and multiple dosing due to the inhibition of CYP2C19 by omeprazole.

Date of literature search: 22 January 2018.

	Phenotype	**Code**	**Gene-drug interaction**	**Action**	**Date**
Dutch Pharmacogenetics Working Group decision	PM	4 AA[#]	yes	no	5 March 2018
	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 thus 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.