CYP2C19: Omeprazole

Amoxi: amoxicillin, AUC: Area under the concentration-time curve, BID: twice a day, CI: confidence interval, Clari: clarithromycin, Clor: oral clearance, EM: extensive metabolizer (*1/*1, sometimes referred to as homozygous EM or homEM in publications, *1/*17), Esome: esomeprazol, GERD: gastroesophageal reflux disease, GIB: gastrointestinal bleeding, Hp: Helicobacter pylori, IM: intermediate metabolizer (*1/*2, *1/*3, sometimes referred to as heterozygous EM or hetEM in publications, *17/*2, *17/*3), Lanso: lansoprazol, Metro: metronidazol, MR: metabolic ratio, NS: not statistically significant, Ome: omeprazol, OR: odds ratio, Panto: pantoprazol, PM: poor metabolizer (*2/*2, *2/*3, *3/*3), PPI: protonpumpinhibitor, Rabe: rabeprazol, S: statistically significant, TID: three times a day, UM: ultrarapid metabolizer (*17/*17).

Results are presented as EM : IM (S or NS compared to EM) : PM (S or NS compared to EM).

Reference	Level of evidence	Clinical relevance	Effect	Remarks
ref. 1 – GERD Saitoh T et al. Influences of CYP2C19 polymorphism on recurrence of reflux esophagitis during proton pump inhibitor maintenance therapy. Hepatogastroenterology 2009;56:703 -6. PMID: 19621685	3	IM: AA PM: AA	28 patients, 8x EM, 14x IM, 6x PM, 39% HP-positive, with initial healing of GERD (judged by endoscopy) after 8 wk treatment with Ome 20 mg/day receive maintenance therapy with Ome 20 mg/day for 6 months. Concomitant medication unknown. EM vs. IM vs. PM: - Recurrence rate of GERD symptoms (%): 50 : 14 (NS) : 17 (NS) - The analysis of the complete group of patients (45x Rabe, 28x omeprazole, 26x Lanso) showed a significantly reduced recurrence rate of GERD symptoms for IM and PM compared to EM. Note: *2 and *3 were genotyped	
ref 2 - GERD Hunfeld NG et al. Effect of CYP2C19*2 and *17 mutations on pharmacodynamics and kinetics of proton pump	4	IM: AA [#]	HP-negative subjects, Ome 10 mg/day (n=11: 5x *1/*1, 1x *1/*17, 1x *2/*17, 4x *1/*2) or Ome 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 vs. *1/*1 (10 mg Ome):	Conclusion authors: 'This study showed that the acid-inhibitory effects of omeprazole in Caucasians were influenced by CYP2C19 status. Due to this effect, single and repeated

inhibitors in Caucasians. Br J Clin Pharmacol 2008;65:752-60. PMID: 18241283			- No statistically significant effect on the percentage of time with intragastric pH > 4 during a 24 hour period on day 1 and day 6. - Ome significantly increases the percentage of time with intragastric pH > 4 on day 1 and day 6 for *1/*2 but not for *1/*1. - Increase of AUC on day 1 and day 6 (NS) *1/*17 vs. *1/*1 (20 mg ome): - No statistically significant effect on the percentage of time with intragastric pH > 4 during a 24 hour period on day 1 and day 6. - Decrease of AUC on day 1 and day 6 (NS) Note: *2, *3, *4, *5, *6, and *17 were genotyped.	administration of omeprazole 10 mg in *1/*1 subjects did not provide significant acid- inhibition when compared with baseline. '
ref. 3 – 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. PMID: 15932363	3	IM: AA PM: AA	119 patients with recurrent reflux esophagitis grade A-D, 46x EM, 53x IM, 20x PM, 75x Hp-neg and 44x Hp- pos, 10-20 mg Ome for 6-12 months. No other acid inhibitory medication. Concomitant medication of influence on CYP2C19 phenotype unknown. EM vs. IM vs. PM: - No statistically significant difference in incidences of adverse events between genotype groups. - Response (%) 6 months: 85.0 : 83.3 (NS) : 83.3 (NS) - Response (%) 12 months: 73.1 : 84.0 (NS) : 80.0 (NS) Note: *2 and *3 were genotyped	Conclusion authors: '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. 4 – 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	3	IM: AA PM: AA	26 patients with reflux esophagitis or ulcera (gastric or duodenal), 6x EM, 10x IM (6x *1/*2, 4x *1/*3), 10x PM (4x *2/*2/, 4x *2/*3, 2x *3/*3), HP status not tested, 20 mg/day Ome for 8 days, no relevant concomitant medication. EM vs. IM vs. PM: - pH day 8: 6.0 : 5.4 (NS) : 6.3 (NS) - Gastrin-AUC (pM.hr): 262 : 255 (NS) : 366 (NS)	AUC compared to EM: IM: 97% PM: 101%

Toxicol 2004;95:112-9. PMID: 15447734			- AUC Ome (nM.hr): 8683 : 8451 (NS) : 8747 (NS) - AUC OH-Ome (nM.hr): 1077 : 1052 (NS) : 381 (S) Note: *2 and *3 were genotyped	
ref. 5 – 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. PMID: 11736724	4	IM: AA [#] PM: AA [#]	15 healthy subjects, 6x EM, 5x IM (4x *1/*2, 1x *1/*3), 4x PM (2x *2/*2, 2x *2/*3), Hp-negative, 20 mg/day Ome for 8 days, no relevant concomitant medication. EM vs. IM vs. PM: - pH day 8: 4.1 : 4.7 (S) : 5.9 (S) - AUC (ng.hr/ml) day 8: 1056.96 : 2417.5 (S) : 7153.0 (S) Note: *2 and *3 were genotyped	AUC compared to EM: IM: 229% PM: 677%
ref. 6 - GERD Sagar M et al. Effects of omeprazole on intragastric pH and plasma gastrin are dependent on the CYP2C19 polymorphism. Gastroenterology 2000;119:670-6. PMID: 10982760	3	IM: AA [#] PM: AA	25 patients, 11x EM 6 Hp-positive, 12x IM (*1/*2) 6 Hp-positive, 2x PM (*2/*2) both Hp-positive. 20 mg Ome single dose. Concomitant medication unknown. EM vs. IM vs. PM: - Percentage time with pH > 4 on day 8: 37.1 : 72.4 (S) : 93.3 (NS) - Gastrin AUC (pM.hr) increase on day 8 compared to baseline: 16 : 184 (S) : 172 (NS) Note: *2 and *3 were genotyped	Conclusion authors: '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 PPI's in a subgroup of patients with H.pylori infection.'
ref. 7 - GERD Furuta T et al. CYP2C19 genotype status and effect of omeprazole on intragastric pH in humans. Clin Pharmacol Ther	3	IM: AA [#] PM: AA [#]	16 healthy subjects, 6x EM, 4x IM (3x *1/*2, 1x *1/*3), 6x PM (4x *2/*3, 2x *2/*2). 20 mg Ome single dose, 1x Hp-positive, no concomitant medication. EM vs. IM vs. PM: - Mean intragastric pH: 2.14 : 3.30 (S) : 4.47 (S) - Gastrin $AUC_{0\text{-}24}$ (pg/ml.hr): 1569 : 1470 (NS) : 2386 (S) - Ome $AUC_{0\text{-}24}$ (ng/ml.hr): 421 : 1403 (NS) : 5109 (S)	

1999;65:552-61. PMID: 10340921			Note: *2 and *3 were genotyped	
ref. 8 – 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. PMID: 14653835	4	IM: AA PM: AA [#]	18 healthy subjects, 6x EM, 6x IM, 6x PM. Crossover design 10 mg/day Ome, 20 mg/day Ome 20 mg/day, or water for 7 days. No concomitant medication. EM vs. IM vs. PM: - Mean intragastric pH after 7 days • Water: 1.6 : 1.6 : 1.7 (NS) • 10 mg Ome: 2.0 : 2.5 (NS): 5.4 (S) • 20 mg Ome: 3.7 : 4.4 (NS): 6.3 (S) - Time (%) with pH > 4 after 7 days: • Water 8 : 11 : 11 (NS) • 10 mg Ome: 23 : 24 (NS): 81 (S) • 20 mg Ome: 46 : 56 (NS): 90 (S) Note: *2 and *3 were genotyped	Conclusion authors: 'Omeprazole 10 mg strongly suppresses acid secretion, but depending on the CYP2C19 genotypes shows greater interindividual variations in suppression than 20 mg.'
ref. 9 – Gastric ulcer/GIB 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. PMID: 17934830	3	IM: AA [#] PM: AA	35 patients with a gastric ulcer, 15x EM, 14x IM, 6x PM. 20 mg Ome for 20 days, 89% Hp-positive. No PPIs, H2-antagonists, NSAIDs, anti-coagulants, corticosteroids, gastrokinetics. Concomitant medication of influence on CYP2C19 phenotype unknown. EM vs. IM vs. PM: - Decrease of ulcer area (%) after 7 days: 46.3 : 61.7 (S): 63.2 (NS) Note: *2 and *3 were genotyped	Conclusion authors: '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. 10 – Gastric ulcer/GIB Sugimoto M et al. Initial 48-hour acid	4	IM: AA [#] PM: AA [#]	15 healthy subjects, 5x EM, 5x IM (4x *1/*2, 1x *1/*3), 5x PM (2x *2/*2, 1x *2/*3, 2x *3/*3), Hp-positive. Crossover design BID 20 mg Ome IV, 10 mg Ome + 10 mg famotidine, or 20 mg Ome + 20 mg famotidine for 2	Conclusion authors: 'This study suggests that the CYP2C19 genotyping test appears to be a useful tool for determining

inhibition by intravenous infusion of omeprazole, famotidine, or both in relation to cytochrome P450 2C19 genotype status. Clin Pharmacol Ther 2006;80:539 -48 PMID: 17112810			days. No concomitant medication. EM vs. IM vs. PM: - Median first 24-hour intragastric pH: • 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 20mg + famotidine 20 mg : 4.8 : 5.8 (S) : 5.8 (S) With neither regimen EMs achieved the required pH for platelet aggregation and blood coagulation (> 5.5). For IM and PM only the 10 mg Ome + 10 mg famotidine was sufficient. With 2 regimes the median pH remained below 4.0 (pH at which fibrin clots are dissolved). - Median second 24-hour intragastric pH: • Ome 20mg: 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) With 2 of the 3 regimens EMs did not achieve the required pH for platelet aggregation and blood coagulation (> 5.5). - Percentage time with pH > 4, 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 with pH > 4, 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 intragastric pH > 5.5 (hr):	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.’

			• 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) - No adverse events were reported for any of the genotypes for any of the regimens Note: *2 and *3 were genotyped	
ref. 11 – Gastric ulcer/GIB 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. PMID: 16911680	3	PM: AA	53 patients with active peptic ulcer, 3x EM, 25x IM, 25x PM. 20 mg / day Ome for 6 weeks. 77% Hp-positive. No H2- antagonist, misoprostol, PPI, sucralfate, corticosteroids, anticholinergics, anti-depressants, antineoplastics or anticoagulants. Other concomitant medication of influence on CYP2C19 phenotype unknown. (EM + IM) vs. PM: - Decrease of ulcer area (%) after 7 days: 48.6 : 50.9 (NS) - Cured after 6 weeks (%): 87.5 : 86.4 (NS) Note: - The EM + IM group mainly consists of IM. - *2 and *3 were genotyped	Conclusion authors: '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. 12 – Gastric ulcer/GIB 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 active gastric ulcer, 6x EM, 18x IM, 7x PM. 20 mg / day Ome for 8 weeks. Approximately 80% Hp-positive. No acid-suppressing drugs, e.g. PPI or H2-antagonist, NSAIDs, anti- coagulants, corticosteroids, gastrokinetic and other drugs to modulate gastrointestinal functions. Other concomitant medication of influence on CYP2C19 phenotype unknown. EM vs. IM vs. PM: - Ulcer size (mm^2) wk 2: 35.8 : 14.6 : 33.9 - Ulcer size (mm^2) wk 8: 5.4 : 0.1 : 0.0	

PMID: 16133961			- 'gastric healing ratio' (%) wk 2: 63.4 : 85.2 (S) : 84.0 (NS) - 'gastric healing ratio' (%) wk 8: 68.8 : 93.8 : 100 Note: *2 and *3 were genotyped	
ref. 13 - Gastric ulcer/GIB 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. PMID: 15447734	3	IM: AA PM: AA	See ref. 4 – GERD	
ref. 14 – 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. PMID: 19166419	3	IM: AA [#] PM: AA [#]	Meta-analysis of 11 studies. Triple therapy (Ome + Amoxi + Clari or Ome + Amoxi + Metro) for 7-14 days. 100% Hp-positive. No prior Hp-treatment. Total number of patients and genotype-distribution not specified. EM vs. IM vs. PM: - Hp eradication rate (OR): 1 : 3.22 (95% CI 1.91-5.42) : 4.28 (95% CI 1.88-9.74)	Conclusion authors: 'The efficacy of omeprazole- and lansoprazole-based first-line triple therapies at the standard doses is dependent on CYP2C19 genotype status.'
ref. 15 – Hp Sugimoto M et al. Influences of proinflammatory and anti-inflammatory cytokine polymorphisms	3	IM: AA [#] PM: AA [#]	360 patients infected with Clari-sensitive Hp, 72x IM, 53x PM. PPI (20 mg BID Ome (n=90) / 30 mg BID Lanso (n=214) / 10 mg BID Rabe (n=56)) + 750 mg BID Amoxi + 400 mg BID Clari for 1 week. Concomitant medication unknown. No association between eradication rate and type of PPI, age or sex.	

on eradication rates of clarithromycin-sensitive strains of Helicobacter pylori by triple therapy. Clin Pharmacol Ther 2006;80:41-50. PMID: 16815316			EM vs. IM vs. PM: - Eradication rate (%): 73.3 : 88.4 (S) : 94.3 (S) - Risk of eradication failure (OR): 1.0 : 0.439 (S) : 0.251 (S) Note: - IL1B-511 genotype is associated with eradication rates in EM. - *2 and *3 were genotyped	
ref. 16 – 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. PMID: 15976989	3	IM: AA [#]	70 patients, 56x EM, 14x IM (*1/*2). 20 mg BID Ome + 1000 mg BID Amoxi + 500 mg BID Clari (n=14) or 40 mg BID Panto + 1000 mg BID Amoxi + 500 mg BID Metro (n=56) for 1 week. Concomitant medication unknown. - Prevalence EMs lower in patients with successful Hp-eradication compared to patients with failure of Hp-eradication (67.6% vs. 91.7% (S)). - Prevalence IMs higher in patients with successful Hp-eradication compared to patients with failure of Hp-eradication (32.4% vs. 8.3% (S)). Note: - In addition to CYP2C19 genotype, Panto/Amoxi/Metro-regime, and MDR1 genotype are also associated with successful eradication. - *2 and *3 were genotyped	
ref. 17 - 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% infected with Clari-sensitive Hp. PPI (20 mg BID Ome (n=100) or 40 mg BID Esome (n=100)) + 1000 mg BID Amoxi + 500 mg BID Clari for 1 week. Use of concomitant CYP2C19 inducers or inhibitors unknown. EM vs. IM vs. PM: - Eradication rate Ome (%): 68.9 : 84.4 : 91.3 (S for trend, int. to treat)	Conclusion authors: '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.'

PMID: 15691303			In the EM group the eradication rate with Esome is increased compared to Ome (OR 4.2 95% CI 1.06-16.65, per protocol). Note: *2 and *3 were genotyped	
ref. 18 - 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. PMID: 15017629	4	IM: AA [#] PM: AA [#]	350 patients, 119x EM, 180x IM, 51x PM. 15% of Hp-isolates Clari- resistant. PPI (20 mg BID Ome (n=175) or 30 mg BID Lanso (n=175)) + 500 mg TID Amoxi + 200 mg TID Clari for 1 week. No concomitant medication. EM vs. IM vs. PM: - Eradication rate Clari-sensitive Hp (%): 72 : 94 : 98 (S) Note: - Eradication rate not quantified individually for Lanso and Ome. - Eradication rate with Clari-resistant Hp is lower compared to Clari-sensitive strains. - IL-1ß-511-genotype is associated with eradication rate in EMs. - *2 and *3 were genotyped	
ref. 19 - Hp Sapone A et al. The clinical role of cytochrome p450 genotypes in Helicobacter pylori management. Am J Gastroenterol 2003;98:1010-5. PMID: 12809821	3	IM: AA [#] PM: AA [#]	143 patients, 116x EM, 25x IM, 2x PM (*2/*2). 20 mg BID Ome + 1000 mg BID Amoxi + 500 mg BID Clari for 1 week. Concomitant medication unknown. EM vs. IM vs. PM: - Phenotype distribution (%) for group with successful eradication: 75.3 : 22.6 : 2.2 - Phenotype distribution (%) for group with failed eradication: 92% : 8% : 0% - EM associated with increased risk for failure of eradication OR univariate analysis 4.34 (95% CI 1.27-4.82). OR multivariate analysis 3.45 (95% CI 1.11-10.70) Note: *2 and *3 were genotyped	
ref. 20 - Hp Miwa H et al.	3	IM: AA	156 patients, 6 lost to follow up, 61x EM, 61x IM, 28x PM. 20 Mg BID Ome + 500 mg Amoxi TID + 200 mg BID	

Clarithromycin resistance, but not CYP2C19 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. PMID: 11713950		PM: AA	Clari for 1 week. Concomitant medication unknown. - No difference in cure rate between genotype groups. Note: *2 and *3 were genotyped	
ref. 21 - 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), amoxycillin and clarithromycin in Japan. Dig Liver Dis 2001;33:671 -5. PMID: 11785712	3	IM: AA PM: AA	170 patiënten, 164 available for analysis, 51x EM, 77x IM, 36x PM. PPI (20 mg BID Ome or 20 mg BID Rabe) + 750 mg BID Amoxi + 400 mg BID Clari for 1 week. Clari-sensitivity unknown. No NSAID or antibiotics other concomitant medication unknown. EM vs. IM vs. PM: - Eradication rate Ome (%): 73.3 : 86.1 (NS) : 85.0 (NS) Note: *2 and *3 were genotyped	
ref. 22- Hp Furuta T et al. Effect of genotypic differences in CYP2C19 on cure rates for Helicobacter pylori	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). PPI (20 mg BID Ome (n=136) or 30 mg BID Lanso (n=135) + 500 mg TID Amoxi + 200 mg TID Clari for 1 week. PPI continued for additional 5-7 weeks. Concomitant medication	Conclusion authors: 'If the CYP2C19 genotype status is determined before treatment, an optimal dose of a PPI may be

infection by triple therapy with a proton pump inhibitor, amoxicillin, and clarithromycin. Clin Pharmacol Ther 2001;69:158 -68. PMID: 11240980			allowed. EM vs. IM vs. PM: - Eradication rate Ome (%): 72.7 : 92.1 (S) : 97.8 (S) Note: - Eradication rate not quantified individually for Lanso and Ome. - *2 and *3 were genotyped	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. 23 - 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. PMID: 10579481	3	PM: AA [#]	108 patients. Dual therapy: 26 patients, 10x EM, 12x IM, 4x PM. 20 mg BID Ome + 500 mg QID Amoxi. Triple therapy: 57 patients, 20x EM, 26x IM, 11x PM. 20 mg BID Ome + 500 mg QID Amoxi + 200 mg QID Clari for 1 week. Quadruple therapy: 25 patients without PPI. Concomitant medication unknown. EM vs. IM vs. PM: - Eradication rate (%) dual therapy: 40 : 41 : 100 (NS) - Eradication rate (%) triple therapy: 75 : 88 : 100 (NS) - Combined analysis of dual and triple therapy: eradication rate larger for PM than for (EM + IM) (S) Note: *2 and *3 were genotyped.	Conclusion authors: '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. 24 - 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. PMID: 10616772	3	IM: AA PM: AA	86 patients. Triple therapy: 44 patients, 35x EM (including 19x IM), 9x PM. 40 mg / day Ome + 2000 mg / day Amoxi + 800 mg /day Clari for 1 week. No NSAIDs, corticosteroids or antibiotics. Other concomitant medication unknown. EM vs. *1/*2 vs. *1/*3 vs. PM: - Eradication rate (%): 81 : 100 (NS) : 75 (NS) : 100 (NS) Note: *2 and *3 were genotyped.	

ref. 25 – Hp Inaba T et al. Randomized open trial for comparison of proton pump inhibitors in triple therapy for Helicobacter pylori infection in relation to CYP2C19 genotype. J Gastroenterol Hepatol. 2002;17:748-53 PMID: 12121503	3	IM: AA PM: AA	58 patients, 21x EM, 27x IM, 10x PM. Clari-sensitive Hp. 20 mg BID Ome + 500 mg TID Amoxi + 200 mg BID Clari for 1 week. Concomitant medication unknown. EM vs. IM vs. PM: - Eradication rate Ome (%): 76.2 : 88.9 (NS) : 90.0 (NS) Note: *2 and *3 were genotyped.	
ref 26 - Pharmacokinetics Rocha A et al. Investigation of the in vivo activity of CYP3A in Brazilian volunteers: comparison of midazolam and omeprazole as drug markers. E ur J Clin Pharmacol 2008;64:901 -6. PMID: 18581106	3	UM: AA	9 healthy subjects, 3x *1/*1, 3x *1/*17, 2x *17/*17, 1x *2/*17. 20 mg Ome single dose after a 12-h fast. No concomitant medication, food or smoking. Plasma concentrations of unchanged omeprazole, hydroxyomeprazole, and omeprazole sulfone were measured in plasma collected 3.5 hr after omeprazole administration. MR Ome/hydroxyOme: (mean (range)) *1/*1: *1/*17: *17/*17: *2/*17: 1,73 (0,93-3,02) 1,18 (0,28-1,91) 0,99 (0,20-1,78) 3,55 (NS) According to the authors all subjects are EM (MR < 4,0). However, MR is determined with healthy subjects including *1/*1, *1/*17 or *17/*17 genotypes. Note: *2, *3, and *17 were genotyped.	

ref 27 - Pharmacokinetics 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. PMID: 18294333	3	UM: A	16 healthy subjects, 11x *1/*1, 5x *17/*17. 40 mg Ome single dose. No concomitant medication or food. Plasma was sampled for up to 10 h post dose. *17/*17 vs. *1/*1: - AUC decreased by 52% (4151 to 1973 hr.nmol/l). (S)) - MR AUC Ome / 5-hydroxyOme decreased by 45% 1,2 to 0.66 (S)) - Decreased interindividual variability for MR (95% CI decreased by 72% from 0.70-1.60 to 0.54-0.79) - Decreased t1/2 Ome (NS) Note: *2, and *17 were genotyped.	Conclusion authors: 'For clinically important drugs that are metabolized predominantly by CYP2C19, the CYP2C19*17 allele might be associated with subtherapeutic drug exposure.'
ref 28 - Pharmacokinetics 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. PMID: 16413245	3	UM: A	107 healthy subjects, 71x *1/*1, 32x *1/*17, 4x *17/*17. 20 mg Ome single dose. MR were calculated from 3-hr post dose plasma samples. *17/*17 vs. *1/*1: - Median MR Ome/5-hydroxyOme decreased by 50% (S; from 0.500 to 0.250). - Predicted mean omeprazole AUC from MR obtained from 24 subjects decreased by 37% (from 1171 to 742 hr.nmol/l). *1/*17 vs. *1/*1 - Median MR Ome/5-hydroxyOme decreased by 19% (S; from 0.500 to 0.405). - Predicted mean omeprazole AUC from MR obtained from 24 subjects decreased by 14% (from 1171 to 1010 hr.nmol/l).	Conclusion authors: '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.'

#: The clinical relevance score was developed to classify negative clinical effects compared to EM. Positive clinical effects are compared to EM are indicated with AA#

Groups at risk	

Remarks
Date literature search: 12 January 2010
Papers with only pharmacokinetic endpoints were excluded for IMs and PMs
Papers with inconsistencies between genotyping and phenotyping were excluded
Papers with eradication therapy with 2 or 4 drugs or a PPI dose lower then the recommended dose in The Netherlands were excluded

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 DPWG: this is in contradiction with the response of Velthuyzen Van Zanten to the meta-analysis by Padol (see below). Effects appear to be related to the type of PPI. Hunfeld et al reported an increased AUC from day 1 to day 5 for Esome but not for Panto. Sakurai et al, 2007, reported no increased AUC from day 1 to 5 for Lanso after IV administration.

Eradication Hp
Meta-analyse [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] provides evidence for an association between CYP2C19 genotype and Hp eradication in primary care. Eradication rates for the individual PPIs, EM vs. IM vs. PM: Ome 62.9 : 76.7 : 92.7, Lanso 74.4 : 82.9 : 87.5, Rabe 77.3 : 85.7 : 80.6. Conclusion authors: '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 Ome 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 fulfill this criterion.'
In a response to Padol et al, Velthuyzen van Zanten S en 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] state that there is evidence of reduced clearance with repeat administrations of PPIs resulting in more profound acid suppression. Therefore, observations after single dose administration cannot be extrapolated to more long-term use.

	Phenotype	Code	Gene-Drug Interaction	Action Required	Date
Decision DPWG	PM	4 AA#	Yes	No	27 May 2010
	IM	4 AA#	Yes	No	
	UM	3 A	Yes	Yes	

#: Denotes positive clinical effect

Action Pharmacy Technician	PM: No action required
	IM: No action required
	UM: Omeprazole metabolism is increased due to genetic variation. Consult pharmacist for dose increase. Dispense and advise the patient to contact prescriber in case of continued acid related complaints.
Action Pharmacist, Physician	PM: No action required
	IM: No action required
	UM: Hp eradication: • Increase dose by 100-200% of the recommended dose • Advise the patient to contact physician in case of insufficient response Other indication: • Be alert to insufficient response • Consider dose increase by 100-200% of the recommended dose • Advise the patient to contact physician in case of insufficient response

Considerations

IM + PM: For IM and PM either a positive clinical effect or no significant difference compared to EM is reported. Increased efficacy for IM and PM in the treatment of GERD, Hp eradication, and Gastric ulcer / GIB suggests that the recommended dose of Ome may be to low for EMs. An increased rate of adverse effects has not been reported for IMs and PMs. However, PM and IM do not show negative clinical effect. Therefore, no adjustment of Ome dose is deemed necessary.

UM: Several papers have reported significant effects on the pharmacokinetics of Ome. To date, no effects on clinical endpoints have been reported. However, for EMs lower efficacy has been reported for the treatment of GERD and Hp eradication compared to IMs and PMs. Therefore it can be anticipated that UMs show lower efficacy. The calculated dose increase is based on the dose increase required to achieve an equal AUC in an EM compared to a PM (1% Roh HK et al., 2004 and 577% Shirai N et al., 2001). For clinical applicability this is translated to a 100-200% dose increase.

Mechanism

Omeprazole is mainly metabolized by CYP2C19 to inactive metabolites. Decreased activity of CYP2C19 results in increased plasma concentrations and an increased AUC. As a result, efficacy and/or adverse event rate may increase. The amount and duration of acid suppression by PPIs is related to the AUC.