CYP2C19: rabeprazole 1856 to 1858

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:
Rabeprazole is primarily converted via a non-enzymatic reduction to a thio-ether compound, which exhibits antimicrobial activity against H. pylori. In addition to this, rabeprazole is converted by CYP2C19 and CYP3A4 to inactive metabolites.
The SPC's and literature studies report an increased AUC for patients with absent CYP2C19 activity (poor metabolisers (PM)) versus patients with normal CYP2C19 activity (extensive metabolisers (EM)). However, in the majority of cases, the observed differences is small (less than 2-fold) and most articles in literature do not support the presence of a significant clinical effect of the CYP2C19 genotype.

IM and PM: In the case of IM and PM, either no significant difference or a positive effect on the result of the treatment with rabeprazole was observed for each of the indication areas. 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 rabeprazole for IM and PM (yes/no-interactions).

UM: There are no data available for UM. For EM, most studies do not support a reduction in effectiveness compared to PM. Of 9 articles on Helicobacter pylori eradication, 8 did not find a signficant effect on effectiveness, including two meta-analyses and a study with 459 patients. This suggest that the reduced effectiveness found in the 9th study with 95 patients was due to a chance finding. Of the 5 studies on ulcers/ bleeding, only the aforementioned study with 95 patients found a significant reduction in effectiveness in ulcer healing. Because in this study, ulcer healing was coupled to Helicobacter pylori eradication, it likely reflects a chance finding. Of 14 studies on GERD/acid inhibition, only 5 found a significantly reduced effectiveness for EM. 4 of these 5 studies examined acid inhibition in healthy volunteers and in two of these the significant effect was not observed for an other rabeprazole dose. In the 5th study an indirect outcome measure, the effectiveness of a PPI-test to distinguish between erosive and non-erosive GERD was examined.
The difference in enzyme activity between PM and EM is larger than between EM and UM. Although it is not possible to say whether UM will exhibit reduced therapeutic effectiveness without further data, the absence of a significant difference in effectiveness between PM and EM makes a significant difference between EM and UM unlikely. Because of the observed kinetic effect and the absence of evidence for a clinical effect, the working group concludes that there is a gene-drug interaction, but that adjustment of therapy is not needed (yes/no-interaction).

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.

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 ulcer/bleeding references, and Hp-references.

<table>
<tr><th>Source</th><th>Code</th><th>Effect</th><th>Comments</th></tr>
<tr><td>ref. 1 - ulcers/bleeding
Nakamura K et al. Limited effect of rebamipide in addition to proton pump inhibitor (PPI) in the treatment of post-endoscopic submucosal dissection gastric ulcers: a randomized controlled trial comparing PPI plus rebamipide combination therapy with PPI monotherapy.
Gut Liver 2016;10:917-924.
PubMed PMID: 27282261.</td><td>3

PM: AA
IM: AA</td><td>106 patients with artificial ulcers due to endoscopic submucosal dissection of early gastric cancer or gastric adenoma were treated with intravenous omeprazole for 2 days, followed by rabeprazole 10 mg/day for 54 days either without (51% of patients) or with rebamipide 100 mg 3 times/day (49% of patients). There were no significant differences in complete ulcer healing between rabeprazole monotherapy and combination therapy, neither for the whole group nor for each phenotype separately. 63% of patients was infected with Helicobacter pylori.
Complete ulcer healing was defined as scar formation.
Use of NSAIDs (including selective COX2-inhibitors or low-dose acetylsalicylic acid) and corticosteroids was excluded. Other relevant co-medication was not excluded.

Genotyping:
- 41x EM
- 48x IM
- 17x PM

Results:
<table><tr><td colspan="2">Complete ulcer healing compared to EM (complete healing in 80% of patients):</td></tr><tr><td>PM</td><td rowspan="2">NS for PM versus IM versus EM</td></tr><tr><td>IM</td></tr></table>
NOTE: Genotyping was performed for *2 and *3. These are the most important gene variants in this Japanese population.</td><td>Authors’ conclusion: ‘It was predicted that a PPI alone may be sufficient for the treatment of post-endoscopic submucosal dissection ulcers in patients classified as PM, whereas the addition of rebamipide may be necessary in patients classified as RM and IM. However, no differences in these subgroups were observed between patients treated with monotherapy and combination therapy.’</td></tr>
<tr><td>ref. 2 - 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 9 randomised controlled trials with in total 13 rabeprazole treatment arms and in total 1260 patients with H. pylori infection treated with triple therapy with rabeprazole, amoxicillin and clarithromycin. 6 of the treatment arms with 40% of the rabeprazole treated patients used rabeprazole 20 mg twice daily. 7 of the treatment arms with 60% of the rabeprazole treated patients used rabeprazole 10 mg twice daily.
Four of the trials in this meta-analysis were also included in this risk analysis separately (Dojo 2001, Inaba 2002, Miki 2003 and Kuwayama 2007).
Five 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:
- 418x EM
- 637x IM
- 205x PM

Results:
<table><tr><td colspan="2">H. pylori eradication rate compared to EM (eradication in 83% of patients; 86% with 20 mg rabeprazole twice daily and 82% with 10 mg twice daily):</td></tr><tr><td>PM</td><td>NS</td></tr><tr><td>IM</td><td>NS</td></tr><tr><td colspan="2">There was no significant heterogeneity between the studies.</td></tr></table></td><td>Authors’ conclusion: ‘No significant differences were observed for rabeprazole or esomeprazole across the CYP-2C19 genotypes of interest.’</td></tr>
</table>

<table>
<tr>
<td>ref. 3 - GERD
Kinoshita Y et al. Randomised clinical trial: a multicentre, double-blind, placebo-controlled study on the efficacy and safety of rabeprazole 5 mg or 10 mg once daily in patients with non-erosive reflux disease. Aliment Pharmacol Ther 2011;33:213-24. PubMed PMID: 21083596.</td>
<td>3

PM: AA
IM: AA</td>
<td>101 patients with non-erosive reflux disease (Los Angeles grade M (minimal changes)), ‘heartburn’ for ≥ 2 days per week, and no response to antacid therapy (1.2 g aluminium hydroxide/magnesium hydroxide 3 times daily after each meal), were treated with rabeprazole 10 mg once daily for 4 weeks. 42% of patients was infected with Helicobacter pylori.
Complete heartburn relief was defined as no episodes of heart burn on the 7 days preceding evaluation.
Use of PPI’s in the 4 weeks preceding treatment, drugs that might affect evaluation of the treatment effects of rabeprazole, Helicobacter pylori eradication therapy, drugs with known interactions with rabeprazole, and need for daily use of NSAIDs, steroids and/or acetylsalicylic acid were excluded. Medications for complications were allowed based on the judgment of the investigators／sub-investigators, but in principle, the dosage and administration method were not allowed to be changed during the study. Co-medication with influence on CYP2C19 was not excluded.

Genotyping:
- 32x EM
- 52x IM
- 17x PM

Results:
<table>
<tr><td colspan="2">Complete heartburn relief compared to EM (complete relief in 44% of patients):</td></tr>
<tr><td>PM</td><td rowspan="2">NS for PM versus IM versus EM</td></tr>
<tr><td>IM</td></tr>
</table>
NOTE: The gene variants for which genotyping was performed were not specified.</td>
<td>Authors’ conclusion: ‘The efficacy of rabeprazole 10 mg was not influenced by age, BMI, hiatal hernia, Helicobacter pylori infection, frequency and severity of heartburn or CYP2C19 genotypes.’</td>
</tr>
<tr>
<td>ref. 4 - ulcer/Hp
Lay CS et al. Correlation of CYP-2C19 genetic polymorphisms with Helicobacter pylori eradication in patients with cirrhosis and peptic ulcer. J Chin Med Assoc 2010;73:188-93. PubMed PMID: 20457439.</td>
<td>3

PM: AA#
IM: AA#</td>
<td>95 patients with cirrhosis and Helicobacter pylori-infected active peptic ulcers were treated with rabeprazole 20 mg, amoxicillin 1000 mg and clarithromycin 500 mg twice daily for 2 weeks, followed by rabeprazole 20 mg once daily for 6 weeks. 48 patients had a gastric ulcer and 47 a duodenal ulcer.
Treatment evaluation was 3 months after the 2-week eradication therapy.
Co-medication was not excluded.

Genotyping:
- 42x EM
- 38x IM
- 15x PM

Results:
<table>
<tr><td colspan="5">PM versus IM versus EM:</td></tr>
<tr><td></td><td></td><td>PM</td><td>IM</td><td>value for EM</td></tr>
<tr><td rowspan="3">% of patients with healed ulcers</td><td>all ulcers</td><td>x 1,2 (S)</td><td>x 1,1 (S)</td><td>80,9%</td></tr>
<tr><td>gastric ulcers</td><td>x 1,3 (S)</td><td>x 1,1 (S)</td><td>80,0%</td></tr>
<tr><td>duodenal ulcers</td><td>x 1,2 (S)</td><td>x 1,1 (S)</td><td>81,8%</td></tr>
<tr><td rowspan="3">% of patients with H. pylori eradication</td><td>all ulcers</td><td>x 1,2 (S)</td><td>x 1,1 (S)</td><td>80,9%</td></tr>
<tr><td>gastric ulcers</td><td>x 1,3 (S)</td><td>x 1,1 (S)</td><td>80,0%</td></tr>
<tr><td>duodenal ulcers</td><td>x 1,2 (S)</td><td>x 1,1 (S)</td><td>81,8%</td></tr>
<tr><td colspan="5">The healing rate of ulcers corresponds with the rate of</td></tr>
</table></td>
<td>Authors’ conclusion: ‘The results of the genotyping test for CYP2C19 seem to predict cure of H. pylori infection and peptic ulcer in patients with cirrhosis who receive triple therapy with rabeprazole, amoxicillin, and clarithromycin.’</td>
</tr>
</table>

ref. 4, continuation		Helicobacter pylori eradication. In patients with Helicobacter pylori eradication, all ulcers were healed. The authors indicated a reduction in Helicobacter pylori eradication in patients with a reduced adherence (100%, 86% and 80% eradication in patients with 100%, 90% and 75% adherence respectively). However, they did not indicate whether adherence differed between EM, IM and PM. NOTE: Genotyping was performed for *2 and *3. These are the most important gene variants in this Taiwanese population.	
ref. 5 - GERD Tseng PH et al. A comparative study of proton-pump inhibitor tests for Chinese reflux patients in relation to the CYP-2C19 genotypes. J Clin Gastroenterol 2009;43:920-5.	3 PM: AA[#]	The aim of this study was to distinguish - based on the reduction in GERD symptoms by rabeprazole - between erosive GERD (usually reduced pH) and non-erosive GERD (less commonly associated with reduced oesophageal pH). 91 patients with erosive oesophagitis (n=51) or non-erosive oesophagitis (n=40), 68x (EM+IM), 12x PM, received rabeprazole 20 mg 2x daily for 2 weeks, co-medication unknown; (EM + IM) versus PM: - accuracy of the PPI test (%): 75.0 : 50.0 (S) The reduced accuracy for PM is caused by the occurrence of false positives. In other words, a reduction in GERD symptoms in patients with non-erosive oesophagitis occurs more often in PM than in EM. NOTE: Genotyping was performed for *2 and *3.	Authors' conclusion: "The clinical application of PPI testing in Chinese patients with reflux may be affected by the CYP2C19 genetic polymorphism, owing to a high possibility of false-positives in patients who metabolized PPI poorly."
ref. 6 - 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	45 patients who were healed of GERD after rabeprazole 10 mg/day for 8 weeks, 10x EM, 28x IM, 7x PM, 42% Hp-pos, received rabeprazole 10 mg/day as maintenance therapy for 6 months, co-medication unknown; EM versus IM versus PM: - frequency of recurrence of GERD symptoms (%): 20: 0 (NS) : 0 (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. 7 - GERD Yamano HO et al. Plasma concentration of rabeprazole after 8-week administration in gastro-esophageal reflux disease patients and intragastric pH elevation. J Gastroenterol Hepatol 2008;23:534-40.	3 IM: AA PM: A	19 Hp-negative patients with reflux oesophagitis (grade M (minimal erosion) or A to C), 5x EM, 8x IM, 6x PM, received rabe 10 mg/day for 8 weeks, co-medication unknown, users of antacids, NSAIDs, anticoagulants, corticosteroids and prokinetics were excluded. EM versus IM versus PM: - % time with intragastric pH > 4: 24 hours: 58.4 : 53.1 (NS) : 71.5 (NS) night: 58.4 : 46.4 (NS) : 72.3 (NS) - median intragastric pH: 4.3 : 3.8 (NS) : 5.2 (NS) - healing of oesophagitis: complete healing or improvement to grade M was achieved in all three genotypes - AUC (ng.h/mL): 375 : 542 (NS) : 957 (S) NOTE: Genotyping was performed for *2 and *3. These are the most common variant alleles in this (ethnically Japanese) population group.	Authors' conclusion: "The AUC of rabeprazole depended on the CYP2C19 genotypes in Japanese GERD patients; however, the intragastric pH elevation was independent of CYP2C19 genotypes."

ref. 8 - GERD Lee YC et al. Influence of cytochrome P450 2C19 genetic polymorphism and dosage of rabeprazole on accuracy of proton-pump inhibitor testing in Chinese patients with gastroesophageal reflux disease. J Gastroenterol Hepatol 2007;22:1286-92.	3 IM: AA PM: AA	63 patients with oesophagitis (25x EM, 28x IM, 10x PM) and 91 patients with endoscopy-negative reflux disease (35x EM, 35x IM, 21x PM), received rabe 20 mg/day (n=74) or rabe 40 mg/day (n=80) for 14 days, PPIs excluded, other co-medication unknown; EM versus IM versus PM: - % oesophagitis patients with 50% reduction in symptoms: 72 : 75 (NS) : 80 (NS) - % patients with endoscopy-negative reflux disease with 50% reduction in symptoms: 43 : 26 (NS) : 29 (NS) - genotypes differed non-significantly in the diagnostic parameters for distinguishing between oesophagitis and endoscopy-negative reflux disease NOTE: Genotyping was performed for *2 and *3.	Authors' conclusion: "Our study demonstrates that rabeprazole-based PPI testing is sensitive and specific for diagnosing GERD, and accuracy is unrelated to CYP2C19 genotype status."
ref. 9 - GERD Li ZS et al. Effect of esomeprazole and rabeprazole on intragastric pH in healthy Chinese: an open, randomized crossover trial. J Gastroenterol Hepatol 2007;22:815-20.	4 IM: AA PM: AA	36 healthy volunteers (9x EM, 19x IM, 8x PM) received rabe 10 mg/day for 5 days, no co-medication; EM versus IM versus PM: - % time with intragastric pH > 4: Day 1: 50.33 : 51.46 (NS) : 67.84 (NS) Day 5: 74.56 : 77.55 (NS) : 85.09 (NS) - median intragastric pH: Day 1: 3.95 : 4.02 (NS) : 5.18 (NS) Day 5: 5.67 : 5.98 (NS) : 6.28 (NS) NOTE: Genotyping was performed for *2 and *3.	Authors' conclusion: "Those who were PM tended to have a higher, albeit not statistically significant, percentage of time with intragastric pH >4 and the median 24-h intragastric pH than those who were EM."
ref. 10 - GERD Ariizumi K et al. Therapeutic effects of 10 mg/day rabeprazole administration on reflux esophagitis was not influenced by the CYP2C19 polymorphism. J Gastroenterol Hepatol 2006;21:1428-34.	3 IM: AA PM: AA	103 patients with reflux oesophagitis grade A-D (36x EM, 50x IM, 17x PM; 39% Hp-positive) received rabe 10 mg/day for 8 weeks, no PPIs or antibiotics, other co-medication unknown; EM versus IM versus PM: - healing of reflux oesophagitis (%): after 4 weeks: 83.3 : 77.3 (NS) : 88.9 (NS) after 8 weeks: 86.1 : 92.0 (NS) : 82.4 (NS) - patients with healing of reflux symptoms after 8 weeks (%): 93.8 : 79.1 (NS) : 81.3 (NS) NOTE: Genotyping was performed for *2 and *3. These are the most common variant alleles in this (ethnically Japanese) population group.	Authors' conclusion: "The results of the present study suggest that, in 10 mg/day rabeprazol administration in the initial therapy, the healing rate of reflux esofagitis was not influenced by the CYP2C19 polymorphism."
ref. 11 - GERD Hu YM et al. Pharmacodynamic and kinetic effect of rabeprazole on serum gastrin level in relation to CYP-2C19 polymorphism in Chinese Hans. World J Gastroenterol 2006;12:4750-3.	4 IM: AA PM: AA	20 healthy volunteers (7x EM, 6x IM, 7x PM; Hp-negative) received rabeprazole 20 mg/day for 8 days, no co-medication; EM versus IM versus PM: - pH on Day 1: 3.82 : 4.36 (NS) : 6.09 (NS) - pH on Day 8: 4.52 : 4.37 (NS) : 5.67 (NS) - gastrin AUC (pg/mL.h) on Day 1: 812.03 : 964.08 (NS) : 1181.06 (NS) - gastrin AUC (pg/mL.h) on Day 8: 1169.98 : 1771.38 (NS) : 1897.45 (NS) - AUC (µg/L.h) on Day 1: 1150.24 : 1539.42 (NS) : 2015.38 (NS) - AUC (µg/L.h) on Day 8: 1145.28 : 1640.91 (NS) : 2495.61 (S) NOTE: Genotyping was performed for *2 and *3.	

ref. 12 - GERD Sugimoto M et al. Comparison of an increased dosage regimen of rabeprazole versus a concomitant dosage regimen of famotidine with rabeprazole for nocturnal gastric acid inhibition in relation to cytochrome P450 2C19 genotypes. Clin Pharmacol Ther 2005;77:302-11.	4 IM: AA PM: AA[#]	15 healthy volunteers (5x EM, 6x IM, 4x PM; Hp-negative) received rabeprazole 20-40 mg/day for 8 days, no co-medication; EM versus IM versus PM: - pH on Day 8, 20 mg: 3.8 : 4.5 (NS) : 6.1 (S) - pH on Day 8, 40 mg: 4.6 : 4.9 (NS) : 6.1 (S) - % time pH> 4.0 on Day 8, 20 mg: 40 : 41.0 (NS) : 89.5 (S) - % time pH> 4.0 on Day 8, 40 mg: 58 : 61.9 (NS) : 87 (S) - incidence of nocturnal heartburn with 20 mg: 100% : 83% (NS) : 25% (NS) - incidence of nocturnal heartburn with 40 mg: 100% : 83% (NS) : 25% (NS) NOTE: Genotyping was performed for *2 and *3. These are the most common variant alleles in this (ethnically Japanese) population group.	
ref. 13 - GERD Sugimoto M et al. Different dosage regimens of rabeprazole for nocturnal gastric acid inhibition in relation to cytochrome P450 2C19 genotype status. Clin Pharmacol Ther 2004;76:290-301.	4 *20 mg* IM: AA PM: AA[#] *40 mg* IM: AA PM: AA[#]	15 healthy volunteers (5x EM, 6x IM (4x *1/*2, 2x *1/*3), 4x PM (1x *2/*2, 2x *2/*3, 1x *3/*3), Hp-neg) received rabeprazole 20-40 mg/day for 8 days, no co-medication; - pH on Day 8, 20 mg: 3.8 : 4.6 (NS) : 6.0 (S) - pH on Day 8, 40 mg: 4.3 : 4.7 (NS) : 5.9 (S) - % time pH> 4.0 on Day 8, 20 mg: 43.7 : 65.7 (NS) : 85.5 (S) - % time pH> 4.0 on Day 8, 40 mg: 56 : 69 (NS) : 91.5 (NS) - AUC_{0-24} (ng.h/mL), 20 mg: 875.5 : 1685.3 (S) : 2276.5 (S) - t½ (h) : 0.93 : 1.00 (NS) : 1.71 (NS) - AUC_{0-24} (ng.h/mL), 40 mg: 1552.2 : 3273.2 (S) : 6646.3 (S) - t½ (h), 40 mg: 0.9 : 0.97 (NS) : 1.71 (S) NOTE: Genotyping was performed for *2 and *3. These are the most common variant alleles in this (ethnically Japanese) population group.	
ref. 14 - GERD Shimatani T et al. Rabeprazole 10 mg twice daily is superior to 20 mg once daily for night-time gastric acid suppression. Aliment Pharmacol Ther 2004;19:113-22.	4 *10 mg 1x daily* IM: AA PM: AA *20 mg 1x daily* IM: AA PM: AA[#] *10 mg 2x daily* IM: AA PM: AA	18 healthy volunteers (6x EM, 6x IM (4x *1/*2, 2x *1/*3), 6x PM (4x *2/*2, 2x *2/*3), Hp-neg) received rabeprazole 10 mg 1x daily or 20 mg 1x daily or 10 mg 2x daily for 7 days, no co-medication; EM versus IM versus PM: *10 mg 1x daily* - pH on Day 7: 3.9 : 4.8 (NS) : 5.0 (NS) - % time pH > 4.0: 49 : 59 (NS) : 71 (NS) *20 mg 1x daily* - pH on Day 7: 4.1 : 5.0 (NS) : 5.8 (S) - % time pH > 4.0: 52 : 67 (NS) : 83 (S) *10 mg 2x daily* - pH on Day 7: 5.4 : 5.6 (NS) : 6.2 (NS) - % time pH > 4.0: 85 : 86 (NS) : 99 (NS) NOTE: Genotyping was performed for *2 and *3. These are the most common variant alleles in this (ethnically Japanese) population group.	
ref. 15 - GERD Shirai N et al. Effects of CYP2C19 genotypic differences in the metabolism of omeprazole and rabeprazole on	4 IM: AA PM: A	15 healthy volunteers (6x EM, 5x IM (4x *1/*2, 1x *1/*3), 4x PM (2x *2/*2, 2x *2/*3), Hp-neg) received rabeprazole 20 mg/day for 8 days, no co-medication; EM versus IM versus PM: - pH on Day 8: 4.8 : 5.0 (NS) : 6.0 (NS) - AUC (ng.h/mL) on Day 8: 463.5 : 1397.9 (NS) : 2437.0 (S)	

intragastric pH. Aliment Pharmacol Ther 2001;15:1929-37.		NOTE: Genotyping was performed for *2 and *3. These are the most common variant alleles in this (ethnically Japanese) population group.	
ref. 16 - GERD Horai Y et al. Pharmacodynamic effects and kinetic disposition of rabeprazole in relation to CYP2C19 genotypes. Aliment Pharmacol Ther 2001;15:793-803.	3 *10 mg* IM: AA PM: AA[#] *20 mg* IM: AA PM: AA	15 healthy volunteers (5x EM, 6x IM (5x *1/*2, 1x *1/*3), 4x PM (3x *2/*2, 1x *3/*3), Hp-neg) received a single dose of rabeprazole 10 or 20 mg, no co-medication; EM versus IM versus PM: *10 mg* - pH on Day 1: 2.88 : 3.12 (NS) : 4.45 (S) - % time pH > 3: 40.8 : 40.8 (NS) : 68 (NS) - AUC_{0-24} (ng.h/mL): 227.8 : 306.2 (S) : 696.5 (S) - Cl_{or} (mL.kg/min): 13.0 : 10.1 (S) : 4.0 (S) - t½ (h) : 0.66 : 0.90 (NS) : 1.69 (NS) *20 mg* - pH on Day 1: 3.34 : 3.97 (NS) : 4.88 (NS) - % time pH > 3: 53 : 65.8 (NS) : 79.8 (NS) - AUC_{0-24} (ng.h/mL): 348.2 : 713.4 (S) : 1512.6 (S) - Cl_{or} (mL.kg/min): 18.7 : 9.9 (S) : 3.6 (S) - t½ (h) : 0.75 : 1.73 (NS) : 1.55 (NS) NOTE: Genotyping was performed for *2 and *3. These are the most common variant alleles in this (ethnically Japanese) population group.	
ref. 17 - GERD Adachi K et al. CYP2C19 genotype status and intragastric pH during dosing with lansoprazole or rabeprazole. Aliment Pharmacol Ther 2000;14:1259-66.	4 IM: AA PM: AA	20 healthy volunteers (7x EM, 9x IM, 4x PM; Hp-neg) received rabeprazole 20 mg/day for 7 days, no co-medication; EM versus IM versus PM: - % nocturnal pH <4: 65.7 : 50.4 (NS) : 52.9 (NS) NOTE: Genotyping was performed for *2 and *3. These are the most common variant alleles in this (ethnically Japanese) population group.	
ref. 18 - 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	39 patients with peptic ulcers (20x EM, 14x IM, 5x PM) received rabeprazole 10 mg 1x daily for 8 weeks, 90% 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: 60.8 : 65.0 (NS) : 55.3 (NS) NOTE: Genotyping was performed for *2 and *3.	Authors' conclusion: "The ulcer improvement ratios did not depend on the CYP-2C19 genotypes."
ref. 19 - 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	50 patients with active peptic ulcers (2x EM, 25x IM, 23x PM) received rabeprazole 10 mg 1x daily for 6 weeks, 75% Hp-pos, no antacid medication, anticoagulants, corticosteroids, 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: 54.1 : 54.9 (NS) - % of healed patients after 6 weeks: 80.8 : 81.0 (NS) Note: the EM + 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. 20 - ulcers/ bleeding	3	39 patients with peptic ulcers (12x EM, 21x IM, 6x PM) received rabeprazole 10 mg/day for 8 weeks, approx. 80% Hp-	

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. **ref. 20, continuation**	IM: AA PM: AA	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: 8.4 : 8.9 (NS) : 18.2 (NS) - ulcer size (mm^2) at week 8: 0.0 : 0.3 (NS) : 0.7 (NS) - gastric healing ratio (%) at week 2: 80.7 : 89.3 (NS) : 84.3 (NS) - gastric healing ratio (%) at week 8: 100 : 90.0 (NS) : 66.7 (NS) Note: Genotyping was performed for *2 and *3. These are the most common variant alleles in this (ethnically Japanese) population group.	

ref. 21 - Hp
Yang JC et al.
Pharmacokinetic-pharmacodynamic analysis of the role of CYP2C19 genotypes in short-term rabeprazole-based triple therapy against Helicobacter pylori.
Br J Clin Pharmacol 2009;67:503-10.
	3
	
	IM: AA
	PM: AA
		48 patients (18x EM, 21x IM and 9x PM, 81% clari-susceptible Hp) received rabeprazole 20 mg 2x daily for 1 week + amoxi 1000 mg 2x daily + clari 500 mg during Days 1-4 or during Days 4-7 or during Days 1-7 (16 patients per treatment), co-medication unknown;
		
		EM versus IM versus PM:
		- eradication % for the three treatments: 71-80 : 43-100 (NS) : 67-100 (NS)
		- population pharmacokinetic model:
		  - addition of CYP2C19 genotype improves the model
		  - improved gastrin response PM versus EM+IM on Day 7 (S)
		  - clearance on Day 7 (L/h): 17.8 : 15.7 (NS) : 9.87 (S)
		
		NOTE: Genotyping was performed for *2 and *3.
			Authors' conclusion: "Helicobacter pylori was eradicated in all CYP2C19 PMs except in one patient infected by a resistant strain, whereas the eradication rates ranged from 58 to 85% in CYP2C19 EMs."

ref. 22 - 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	Meta-analysis of 6 studies with triple therapy (rabe + amoxi + clari or rabe + amoxi + metro) for 1-2 weeks in Hp-positive patients who had not previously received eradication therapy. n = 860 (279x EM, 444x IM, 137x PM). EM versus IM versus PM: - no significant differences in eradication %.	Authors' conclusion: "The efficacy of omeprazole- and lansoprazole-based first-line triple therapies at the standard doses is dependent on CYP2C19 genotype status, which appears not to affect the efficacy of the regimens including rabeprazole."
ref. 23 - Hp Kuwayama H et al. Rabeprazole-based eradication therapy for Helicobacter pylori: a large-scale study in Japan. Aliment Pharmacol Ther 2007;25:1105-13.	3 IM: AA PM: AA	459 patients (149x EM, 230x IM and 80x PM, 67% clari-susceptible Hp) received rabe 10 mg + amoxi 750 mg + clari 200 mg (n=119) or rabe 10 mg + amoxi 750 mg + clari 400 mg (n=109) or rabe 20 mg + amoxi 750 mg + clari 200 mg (n=116) or rabe 20 mg + amoxi 750 mg + clari 400 mg (n=115) 2x daily for 1 week. For patients with open ulcers, this treatment was followed by rabe 10 mg/day for 7 weeks (peptic ulcer) or 5 weeks (duodenal ulcer). NSAIDs, antacids, bismuth, antiprotozoa, antibiotics, M1-receptor antagonists, oral corticosteroids or immunostimulants were excluded, other co-medication unknown; EM versus IM versus PM: - eradication %: 86 : 89 (NS) : 96 (NS) - eradication % for the 4 treatments: 83-88 : 84-93 (NS) : 94-100 (NS) (EM+ IM) versus PM: - eradication % clari-susceptible Hp: 94 : 99 (NS)	Authors' conclusion: "Rabeprazole-based triple therapy achieved good eradication of clarithromycin-resistant strains even in EM patients."

ref. 23, continuation		- eradication % clari-resistant Hp: 49 : 60 (NS) NOTE: Genotyping was performed for *2 and *3. These are the most common variant alleles in this (ethnically Japanese) population group.	
ref. 24 - Hp Miki I et al. Impact of clarithromycin resistance and CYP2C19 genetic polymorphism on treatment efficacy of Helicobacter pylori infection with lansoprazole- or rabeprazole-based triple therapy in Japan. Eur J Gastroenterol Hepatol 2003;15:27-33.	3 IM: AA PM: AA	40 patients (12x EM, 23x IM and 5x PM, 100% clari-susceptible Hp, no amoxi-resistance) received rabe 20 mg + amoxi 750 mg + clari 400 mg 2x daily for 1 week, co-medication unknown; EM versus IM versus PM: - eradication %: 91.7 : 100 (NS) : 100 (NS) NOTE: Genotyping was performed for *2 and *3.	
ref. 25 - 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.	3 IM: AA PM: AA	78 patients (21x EM, 41x IM and 16x PM) received rabe 20 mg + amoxi 750 mg + clari 400 mg 2x daily for 1 week, clari-resistance of Hp unknown, no use of NSAIDs or antibiotics, other co-medication unknown; EM versus IM versus PM: - eradication %: 81.0 : 82.9 (NS) : 87.5 (NS) NOTE: Genotyping was performed for *2 and *3. These are the most common variant alleles in this (ethnically Japanese) population group.	
ref. 26 - Hp Hokari K et al. Efficacy of triple therapy with rabeprazole for Helicobacter pylori infection and CYP2C19 genetic polymorphism. Aliment Pharmacol Ther 2001;15:1479-84.	3 PM: AA	88 patients (75x EM, 13x PM) received rabe 10 mg 1x daily or 10 mg 2x daily or 20 mg 2x daily + amoxi 750 mg 2x daily + clari 200 mg 2x daily for 1 week, clari-resistance of Hp unknown, no NSAIDs, anticoagulants or corticosteroids, other co-medication unknown; EM versus PM: - eradication %: 86.5: 76.9 (per protocol analysis, difference NS) Note: percentages were not broken down according to the 3 rabeprazole doses. Strange that PM has a lower healing percentage. Note: Genotyping was performed for *2 and *3. These are the most common variant alleles in this (ethnically Japanese) population group.	
ref. 27 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	63 patients (24x EM, 31x IM, 8x PM; clari-susceptible Hp) received rabe 10 mg 2x daily + amoxi 500 mg 3x daily + clari 200 mg 2x daily for 1 week, co-medication unknown; EM versus IM versus PM: - eradication %: 62.5 : 87.1 (NS) : 87.5 (NS) NOTE: Genotyping was performed for *2 and *3. These are the most common variant alleles in this (ethnically Japanese) population group.	

ref. 28 SPC Pariet (rabeprazole) 16-02-17.	0 PM: A	CYP2C19 polymorphism: Following a daily dose of 20 mg rabeprazole sodium for 7 days, the AUC and the half-life for slowly metabolising CYP-2C19 genotypes were 1.9 and 1.6 times higher respectively than the corresponding parameters for rapidly metabolising genotypes, whilst the C_{max} had increased by only 40%.	
ref. 29 SPC Aciphex (rabeprazole sodium), USA, 24-10-16.	0 PM: A	Pharmacogenomics: In a clinical study in evaluating Aciphex delayed-release tablets in Japanese adult patients categorized by CYP2C19 genotype (n=6 per genotype category), gastric acid suppression was higher in poor metabolizers as compared to extensive metabolizers. This could be due to higher rabeprazole plasma levels in poor metabolizers. The clinical relevance of this is not known. Whether or not interactions of rabeprazole sodium with other drugs metabolized by CYP2C19 would be different between extensive metabolizers and poor metabolizers has not been studied. Pharmacokinetics: CYP2C19 exhibits a known genetic polymorphism due to its deficiency in some sub-populations (e.g., 3 to 5% of Caucasians and 17 to 20% of Asians). Rabeprazole metabolism is slow in these sub-populations, therefore, they are referred to as poor metabolizers of the drug.	

[#] 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	-

Comments:

- Of the articles published after January 2010, only articles were included with data on UM patients or with data on more than 50 patients with ulcers or bleeding, more than 100 patients with gastroesophageal reflux disease or more than 400 patients with Helicobacter infection. Other articles did not add enough to the evidence to be included.
  A study with 26 healthy volunteers showing an increase in rabeprazole exacerbation of celecoxib-induced small bowel injury for PM in comparison to IM+EM was not included. The interaction between rabeprazole and celecoxib is not included in the KNMP database, suggesting this to be a clinically unimportant interaction. In addition, for EM, a reduced effectiveness of acid inhibition was only observed in healthy volunteers, not in large patient studies. This questions the clinical importance of studies in healthy volunteers.
  Studies with only kinetic endpoints were not included.
  Studies with eradication therapy based on 2 or 4 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.

Date of literature search: 23 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	--	Yes	No	

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

Mechanism:
Rabeprazole is primarily converted via a non-enzymatic reduction to a thio-ether compound, which exhibits antimicrobial activity against H. pylori. In addition to this, rabeprazole is converted by CYP2C19 and CYP3A4 to inactive metabolites. A reduced activity of CYP2C19 results in higher plasma concentrations and a higher AUC of rabeprazole and can therefore result in improved therapeutic effectiveness and/or more side effects. The extent and duration of effective acid inhibition by proton pump inhibitors is dependent on the AUC.