CYP2C19: rabeprazole 2513 to 2515

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

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 SmPCs and literature report an increased AUC and decreased clearance for individuals with absent CYP2C19 activity (poor metabolisers (PM)) versus individuals with normal CYP2C19 activity (normal metabolisers (NM)) (SmPC Pariet 30-09-2023, SmPC Aciphex, USA, 18-07-2023, Yamano 2008, Hu 2006, Sugimoto 2004, Shirai 2001, Horai 2001, and Yang 2009). However, the Dutch SmPC reports the observed differences to be 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 (no significant difference in all 5 meta-analyses and 6 out of 7 studies for Helicobacter pylori eradication (Zhao 2022, Morino 2021, Fu 2021, Tang 2013, Zhao 2008, Yang 2009, Kuwayama 2007, Miki 2003, Dojo 2001, Hokari 2001, and Inaba 2002), 6 out of 7 studies for gastroesophageal reflux disease (Kinoshita 2018, Kinoshita 2011, Saitoh 2009, Yamano 2008, Lee 2007, Ariizumi 2006)), and in 5 out of 6 studies for ulcer healing (Zhu 2022, Nakamura 2016, Ando 2008, Ji 2006, Ando 2005), and for gastric acid suppression (5 out of 9 studies (Yamano 2008, Li 2007, Hu 2006, Shirai 2001, Adachi 2000)). The only study investigating side effects, did not find an increase for PM (Fukui 2024). Because of the observed kinetic effect, the KNMP Pharmacogenetics Working Group concluded that there is a gene-drug interaction. However, due to the absence of negative effects, it is not useful or necessary to modify the treatment with rabeprazole for IM and PM (yes/no-interactions).

UM: There are no data available for UM. For NM, most studies do not support a reduction in effectiveness compared to PM. Of 12 articles on Helicobacter pylori eradication, 11 did not find a significant effect on effectiveness, including five meta-analyses and a study with 459 patients (Zhao 2022, Morino 2021, Fu 2021, Tang 2013, Zhao 2008, Yang 2009, Kuwayama 2007, Miki 2003, Dojo 2001, Hokari 2001, and Inaba 2002). This suggest that the reduced effectiveness found in the 9th study with 95 patients (Lay 2010) was due to a chance finding. Of the 6 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 16 studies on GERD/ acid inhibition, only 5 found a significantly reduced effectiveness for NM. 4 of these 5 studies examined acid inhibition in healthy volunteers (Sugimoto 2005, Sugimoto 2004, Shimatani 2004, and Horai 2001) and in two of these the significant effect was not observed for another rabeprazole dose (Shimatani 2004 and Horai 2001). In the 5th study (Tseng 2009) 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 NM is larger than between NM 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 NM makes a significant difference between NM and UM unlikely. Because of the observed kinetic effect and the absence of evidence for a clinical effect, the KNMP Pharmacogenetics Working Group concluded 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 in the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

The table below follows the KNMP definitions for NM, PM, IM and UM. The definitions of NM, PM, IM and UM used in the table below may therefore differ from the definitions used by the authors in the article.

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

For the period after 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.

Source	Code	Effect	Comments
ref. 1, treatment > 30 days Fukui R et al. Relationships of proton pump inhibitor-induced renal injury with CYP2C19 polymorphism: a retrospective cohort study. Clin Pharmacol Ther 2024;115:1141-51. PMID: 38258325.	3 PM: AA	123 patients were treated with rabeprazole for at least 30 days. Follow-up was for 180 days after treatment initiation. Administration of rabeprazole was for a period of 32-5,829 days (median 520 and 443 days for non-PM and PM, respectively, so longer than the follow-up period). PM patients were more often administered omeprazole within 7 days before the start of rabeprazole than non-PM patients (17.6% versus 2.8%). Patients were excluded if they had a history of kidney disease, received dialysis or continuous haemodialysis and filtration during the observation period, had a very high eGFR (> 125 mL/min/1.73 m^2), or had muscle weakness. Co-medication with CYP2C19 inhibitors and inducers, and with drugs affecting kidney function was not excluded. Neither was the use of other PPIs within 7 days before the start of esomeprazole. Genotyping: - 46x NM - 60x IM - 17x PM Results: PM versus IM+NM: time to a 30% decrease in eGFR: NS NOTE: Genotyping was for *2, *3, and *17. These are the most important gene variants in this Japanese population.	Authors' conclusion: 'This retrospective study showed that CYP2C19 metabolizer status was associated with the time to a 30% eGFR decrease in patients treated with lansoprazole, but not with esomeprazole, rabeprazole, or vonoprazan.'
ref. 2 - ulcers/bleeding Zhu H et al. Effect and safety of anaprazole in the treatment of duodenal ulcers: a randomized, rabeprazole-controlled, phase III non-inferiority study. Chin Med J (Engl) 2022;135:2941-9. PMID: 36580650.	4 PM: AA IM: AA	92 patients with duodenal ulcers started treatment with rabeprazole 10 mg once daily for 4 weeks. Treatment was per-protocol in 95% of patients. 82% of patients was infected with Helicobacter pylori. Use of PPIs within 5 days before treatment or for >3 consecutive days within 28 days before treatment; triple or quadruple anti-H. pylori therapy within 28 days of treatment; and use of drugs that can cause ulcers or bleeding ulcers (e.g., systemic glucocorticoid therapy, nonsteroidal anti-inflammatory drug, and anticoagulants) for >3 consecutive days within 28 days before treatment were excluded. During rabeprazole treatment, histamine H2 receptor antagonists and drugs that may interact with PPIs were not allowed. Genotyping: - 42x NM - 40x IM - 10x PM Results: Ulcer healing rate compared to NM (ulcer healing in 95.2% of patients): PM: NS for PM versus IM versus NM IM NOTE: The authors state that fluorescence polymerase chain reaction (PCR) and Sanger sequencing were used to	Authors' conclusion: 'Healing rates did not significantly differ by H. pylori status or CYP2C19 genotype.'

<table>
<tr><td>ref. 2, continuation</td><td></td><td>detect CYP2C19 polymorphisms, but do not state which part(s) of the gene were amplified by PCR. So, it is not known which parts of the gene have been sequenced and therefore which gene variants and thereby alleles were investigated. Neither do the authors state how genotypes were translated to phenotypes. Because only 3 genotypes were mentioned, including IM and PM, at least one absent function or reduced function allele should have been determined and found. The ratio of NM:IM:PM observed is similar to the ratio found in East-Asians if both *2 and *3 are determined. These are the most important gene variants in this Chinese population.</td><td></td></tr>
<tr><td>ref. 3, Hp
Zhao X et al.
Effects of CYP2C19 genetic polymorphisms on the cure rates of H. pylori in patients treated with the proton pump inhibitors: An updated meta-analysis.
Front Pharmacol 2022;13:938419.
PMID: 36278195.</td><td>3

PM: AA
IM: AA</td><td>Meta-analysis of 12 clinical trials or randomised controlled trials with a total of 1626 patients (590 NM, 780 IM, and 256 PM) with H. pylori infection treated with triple therapy with rabeprazole. Rabeprazole doses in the trials were not mentioned.
Four of the studies in this meta-analysis were also included in this risk analysis separately (Kuwayama 2007, Miki 2003, Inaba 2002, and Dojo 2001).
Of the studies in this meta-analysis, 11 were also included in the meta-analysis by Fu 2021, 8 in the meta-analysis by Morino 2021, 7 in the meta-analysis by Tang 2013, and 5 in the meta-analysis by Zhao 2008.
Meta-analyses were performed with a random-effects model in case of significant heterogeneity between the studies and with a fixed-effect model in case of low heterogeneity between the studies. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised.
Considering quality of the included studies, only randomisation and blindness (single and double blindness either to treatment or genotype group) were considered. In addition, the results were not reported.
Publication bias analysis was only performed for all studies (all PPIs), not for the subgroup of rabeprazole studies.

Results:<table><tr><td colspan="2">H. pylori eradication rate compared to NM (eradication in 83.7% of patients):</td></tr><tr><td>PM</td><td>NS</td></tr><tr><td>IM</td><td>NS</td></tr><tr><td colspan="2">For both comparisons, there was no significant heterogeneity between the studies.</td></tr></table></td><td>Authors’ conclusion: ‘There was a significantly lower H. pylori cure rate in NM subjects than that in IM subjects when treated with omeprazole and lansoprazole, but not rabeprazole, esomeprazole, or pantoprazole.’</td></tr>
<tr><td>ref. 4, Hp
Morino Y et al.
Influence of cytochrome P450 2C19 genotype on Helicobacter pylori proton pump inhibitor-amoxicillin-clarithromycin eradication therapy: a meta-analysis.
Front Pharmacol 2021;12:759249.
PMID: 34721043.</td><td>3</td><td>Meta-analysis of 10 randomised controlled trials with a total of 1706 patients (626 NM, 833 IM, and 247 PM) with H. pylori infection treated with rabeprazole/amoxicillin/clarithromycin triple therapy. The rabeprazole dose used was 20 mg (4 studies), either 20 or 10 mg (2 studies) or 10 mg (4 studies) twice a day. Treatment duration was 1 week in nine studies and 2 weeks in one study (using 20 mg rabeprazole).
Four of the studies in this meta-analysis were also included in this risk analysis separately (Kuwayama 2007, Miki 2003, Inaba 2002, and Dojo 2001).
Of the studies in this meta-analysis, 9 were also included in the meta-analysis by Fu 2021, 7 in the meta-analysis by Tang 2013, and 5 in the meta-analysis by Zhao 2008.
Meta-analyses were performed with a random-effects model in case of significant heterogeneity between the studies and with a fixed-effect model in case of low heterogeneity between the studies. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was stan-</td><td>Authors’ conclusion: ‘The cure rate of omeprazole and lansoprazole-containing eradication regimens differed among CYP2C19 genotypes, while that of rabeprazole and esomeprazole-containing regimens was similar.’</td></tr>
</table>

<table>
<tr><td>ref. 4, continuation</td><td>IM: AA
PM: AA</td><td>dardised.
Quality of the included studies was not assessed.
Publication bias analysis was performed by funnel plot only and only for all studies (all PPIs), not for the subgroup of rabeprazole studies.

Results:<table><tr><td colspan="2">H. pylori eradication rate compared to NM (eradication in 83.7% of patients):</td></tr><tr><td>IM</td><td>NS</td></tr><tr><td>PM</td><td>NS</td></tr><tr><td colspan="2">For both comparisons, there was no significant heterogeneity between the studies.</td></tr></table></td><td></td></tr>
<tr><td>ref. 5, Hp
Fu J et al.
The effect of CYP-2C19 gene polymorphism on the eradication rate of Helicobacter pylori by proton pump inhibitors-containing regimens in Asian populations: a meta-analysis.
Pharmacogenomics 2021;22:859-79.
PMID: 34414773.</td><td>3</td><td>Meta-analysis of 20 Asian studies (including 14 randomised controlled trials and 5 cohort studies) with a total of 2295 patients (908 NM, 1044 IM, and 343 PM) with H. pylori infection treated with triple or quadruple therapy. One of the included studies (Isomoto et al. (Japan), probably Isomoto 2003 comparing dual therapy with rabeprazole 20 mg twice a day during 2 weeks with triple therapy with rabeprazole 10 mg twice a day during 1 week) is not described in the article.
One of the included studies did not report data for rabeprazole and esomeprazole separately (Lee VWY et al. 2010)
The rabeprazole dose used in the 19 described studies was 20 mg twice a day in 7 studies (during 1 week in 4 studies and during 2 weeks in 3 studies), 10 mg twice a day in 10 studies (during 1 week in 9 studies and during 10 days in 1 study), and either 20 or 10 mg twice a day during 1 week in 2 studies. One of the included studies, investigating a total of a total of 84 patients (36 NM, 35 IM, and 13 PM), used quadruple therapy. Of the 123 patients in Isomoto 2003, 63 (40 NM, 16 IM, and 7 PM) received dual therapy. All included studies were assessed as low risk of bias using the Cochrane bias risk assessment tool (based on scoring low, uncertain or high risk of bias in 7 domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias) or as high or medium quality (scoring > 6 or 4-6 of the maximum of 9 points on the Newcastle-Ottawa Scale, respectively). Results were described for all studies except for Isomoto 2003. Three of the fourteen described randomised trials had a low risk of bias in 5 domains and an uncertain risk in two domains, four had a low risk of bias in 4 domains and an uncertain risk in 3 domains, two had a low risk of bias in 3 domains and an uncertain risk in 4 domains, three had a low risk of bias in 4 domains, an uncertain risk in 2 domains and a high risk in one domain, one had a low risk of bias in 3 domains, an uncertain risk in 3 domains and a high risk in one domain, and the fourteenth had a low risk of bias in 3 domains, an uncertain risk in 2 domains and a high risk in 2 domains.
Two of the five described cohort studies scored 7 points on the Newcastle-Ottawa Scale, two 6 points and the fifth 5 points.
Four of the studies in this meta-analysis were also included in this risk analysis separately (Kuwayama 2007, Miki 2003, Inaba 2002, and Dojo 2001).
Of the studies in this meta-analysis, 9 were also included in the meta-analysis by Tang 2013 and 6 in the meta-analysis by Zhao 2008.
Meta-analyses were performed with a random-effects model, but prospective registration of the protocol was not mentio-</td><td>Authors' conclusion: 'Rabeprazole-, esomeprazole- and pantoprazole-based eradication program was less affected by the CYP2C19 polymorphism.'</td></tr>
</table>

<table>
<tr>
<td>ref. 5, continuation</td>
<td>IM: AA
PM: AA</td>
<td>ned. The search and selection strategy was transparent and the data extraction was standardised.
Publication bias analysis was only performed for all studies (all PPIs), not for the subgroup of rabeprazole studies. For all PPIs, there was publication bias for the comparison of PM and NM.

Results:
<table>
<tr><td colspan="2">H. pylori eradication rate compared to NM (eradication in 79.4% of patients):</td></tr>
<tr><td>IM</td><td>NS</td></tr>
<tr><td>PM</td><td>NS</td></tr>
<tr><td colspan="2">For both comparisons, heterogeneity between the studies was very low and not significant.</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>ref. 6 - GERD
Kinoshita Y et al. Efficacy and safety profile of Z-215 (azeloprazole sodium), a proton pump inhibitor, compared with rabeprazole sodium in patients with reflux esophagitis: a phase II, multicenter, randomized, double-blind, comparative study.
Curr Ther Res Clin Exp 2018;88:26-34.
PMID: 30038671.</td>
<td>3

PM: AA
IM: AA</td>
<td>126 patients with reflux oesophagitis (20.6% Los Angeles grade C/D, i.e. severe oesophagitis, 77.8% grade A/B, and 1.6% grade N/M, i.e. no mucosal breaks) started treatment with rabeprazole 10 mg once daily for 8 weeks. Patients whose mucosal break had healed (Grade N/M) after 4 weeks were permitted to discontinue rabeprazole at that time. 11.9% of patients was infected with Helicobacter pylori. Endoscopic healing rate was determined after 8 weeks.
The amount of gastrin secretion depends on the amount of gastric acid secretion (increase in gastrin levels with a decrease in gastric acid secretion).
Use of PPI’s in the 2 weeks before and of any drugs for reflux oesophagitis in the week before the screening period of the study was excluded. During the study period, drugs for reflux oesophagitis and symptom improvement, CYP3A4 inhibitor/inducers, and bisphosphonate drugs were excluded, but CYP2C19 inhibitors or inducers were not.

Genotyping:
- 40x NM
- 64x IM
- 22x PM

Results:
<table>
<tr><td colspan="3">Result for PM versus IM versus NM:</td></tr>
<tr><td></td><td></td><td>value for NM</td></tr>
<tr><td>endoscopic healing rate</td><td>NS</td><td>97.5%</td></tr>
<tr><td></td><td>Results were also NS if the healing rate was assessed by an Independent Adjudication Committee, consisting of 3 experts in the field.</td><td></td></tr>
<tr><td>serum gastrin levels</td><td>The serum gastrin level of PM tended to be higher than that of NM and IM at the final observation point (NS) (significance not mentioned).</td><td>approx. 175 pg/ml</td></tr>
</table>

NOTE: The gene variants for which genotyping was performed were not specified, neither was the genotype-phenotype translation used.</td>
<td>Authors’ conclusion: ‘We also showed that CYP2C19 genotype does not influence the efficacy of 10 mg rabeprazole. On the other hand, whereas serum gastrin levels in the Z-215 groups were not influenced by CYP2C19 genotype, those in the 10-mg rabeprazole group were.’</td>
</tr>
<tr>
<td>ref. 7 - ulcers/bleeding
Nakamura K et al. Limited effect of rebamipide in addition to proton pump inhibitor (PPI) in the</td>
<td>3</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</td>
<td>Authors’ conclusion: ‘It was predicted that a PPI alone may be sufficient for the treatment of post-endoscopic submucosal dissection ul-</td>
</tr>
</table>

<table>
<tr>
<td>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.

ref. 7, continuation</td>
<td>PM: AA
IM: AA</td>
<td>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 NM
- 48x IM
- 17x PM

Results:
<table>
<tr><td colspan="2">Complete ulcer healing compared to NM (complete healing in 80% of patients):</td></tr>
<tr><td>PM</td><td rowspan="2">NS for PM versus IM versus NM</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>cers 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. 8 - Hp
Tang HL et al. Effects of CYP2C19 loss-of-function variants on the eradication of H. pylori infection in patients treated with proton pump inhibitor-based triple therapy regimens: a meta-analysis of randomized clinical trials.
PLoS One 2013;8:e62162.
PubMed PMID: 23646118.</td>
<td>3

PM: AA
IM: AA</td>
<td>Meta-analysis of 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. Risk of bias was high in four of the included studies, unclear in four studies and low in the nineth study according to the Cochrane risk of bias tool by the following dominions: randomization method, allocation concealment, blinding, incomplete outcome data addressed and selective reporting.
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).
Six of the trials in this meta-analysis were also included in the meta-analysis of Zhao 2008.
If heterogeneity between the studies was not significant, a fixed effects model was used first. Results were confirmed by using a random effects model. This indicates that the initially used statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised.
Possible publication bias was only analysed if there were more than ten studies included in the meta-analysis, so not for rabeprazole.

Genotyping:
- 418x NM
- 637x IM
- 205x PM

Results:
<table>
<tr><td colspan="2">H. pylori eradication rate compared to NM (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. 9 - 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 NM
- 52x IM
- 17x PM

Results:
<table>
<tr><td colspan="2">Complete heartburn relief compared to NM (complete relief in 44% of patients):</td></tr>
<tr><td>PM</td><td rowspan="2">NS for PM versus IM versus NM</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. 10 - 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 NM
- 38x IM
- 15x PM

Results:
<table>
<tr><td colspan="5">PM versus IM versus NM:</td></tr>
<tr><td></td><td></td><td>PM</td><td>IM</td><td>value for NM</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. 10, 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 NM, IM and PM. NOTE: Genotyping was performed for *2 and *3. These are the most important gene variants in this Taiwanese population.	
ref. 11 - 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 (NM+IM), 12x PM, received rabeprazole 20 mg 2x daily for 2 weeks, co-medication unknown; (NM + 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 NM. 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. 12 - 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 NM, 28x IM, 7x PM, 42% Hp-pos, received rabeprazole 10 mg/day as maintenance therapy for 6 months, co-medication unknown; NM 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 NM. NOTE: Genotyping was performed for *2 and *3.	
ref. 13 - 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 NM, 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. NM 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. 14 - 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 NM, 28x IM, 10x PM) and 91 patients with endoscopy-negative reflux disease (35x NM, 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-medica-tion unknown; NM 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. 15 - 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 NM, 19x IM, 8x PM) received rabe 10 mg/day for 5 days, no co-medication; NM 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 NM."
ref. 16 - 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 NM, 50x IM, 17x PM; 39% Hp-positive) received rabe 10 mg/day for 8 weeks, no PPIs or antibiotics, other co-medication unknown; NM 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. 17 - 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 NM, 6x IM, 7x PM; Hp-negative) received rabeprazole 20 mg/day for 8 days, no co-medication; NM 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. 18 - 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 NM, 6x IM, 4x PM; Hp-negative) received rabeprazole 20-40 mg/day for 8 days, no co-medication; NM 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. 19 - 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 NM, 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. 20 - 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 NM, 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; NM 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. 21 - 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 NM, 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; NM 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. 22 - 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 NM, 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; NM 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. 23 - 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 NM, 9x IM, 4x PM; Hp-neg) received rabeprazole 20 mg/day for 7 days, no co-medication; NM 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. 24 - 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 NM, 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 CYP2C19 unknown. NM 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 CYP2C19 genotypes."
ref. 25 - 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 NM, 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. (NM + 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 NM + IM group consisted primarily of IM Note: Genotyping was performed for *2 and *3.	Authors' conclusion: "CYP2C19 genotypes had no effect on the remaining ratio of peptic ulcers after 1 week and the healing rate of peptic ulcers after 6 weeks."
ref. 26 - ulcers/ bleeding	3	39 patients with peptic ulcers (12x NM, 21x IM, 6x PM) received rabeprazole 10 mg/day for 8 weeks, approx. 80%	

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. 26, continuation**	IM: AA PM: AA	Hp-pos, no antacid medication, NSAIDs, anticoagulants or corticosteroids, co-medication with an effect on CYP2C19 unknown. NM 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. 27 - 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 NM, 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;
		
		NM 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 NM+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 NMs."

ref. 28 - 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. The total number of patients in the meta-analysis was 860 (279x NM, 444x IM, 137x PM). Only studies with a Jadad quality assessment score ≥ 2 were included. The following two parameters were also considered: randomisation and blindness (double or single blindness either to treatment or genotype groups). However, the results of the quality assessments were not reported. Four of the studies in the meta-analysis were included in this risk analysis separately (Kuwayama 2007, Miki 2003, Inaba 2002, and Dojo 2001). Meta-analyses were performed with a random-effects model in case of significant heterogeneity between the studies and with a fixed-effect model in case of low heterogeneity between the studies. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised. Publication bias analysis was not performed. NM versus IM versus PM: - 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. 29 - Hp Kuwayama H et al. Rabeprazole-based eradication therapy for Helicobacter pylori: a large-scale	3	459 patients (149x NM, 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,	Authors' conclusion: "Rabeprazole-based triple therapy achieved good eradication of clarithromycin-resistant strains

study in Japan. Aliment Pharmacol Ther 2007;25:1105-13. **ref. 29, continuation**	IM: AA PM: AA	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; NM versus IM versus PM: - eradication %: 86 : 89 (NS) : 96 (NS) - eradication % for the 4 treatments: 83-88 : 84-93 (NS) : 94-100 (NS) (NM+ IM) versus PM: - eradication % clari-susceptible Hp: 94 : 99 (NS) - 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.	even in NM patients.”
ref. 30 - 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 NM, 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; NM versus IM versus PM: - eradication %: 91.7 : 100 (NS) : 100 (NS) NOTE: Genotyping was performed for *2 and *3.	
ref. 31 - 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 NM, 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; NM 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. 32 - 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 NM, 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; NM 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	

ref. 32, continuation		the most common variant alleles in this (ethnically Japanese) population group.	
ref. 33 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 NM, 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; NM 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. 34 SmPC Pariet (rabeprazole) 30-09-23.	0 PM: A	CYP2C19 polymorphism: Following a daily dose of 20 mg rabeprazole sodium for 7 days, the AUC and the half-life for poor metabolising CYP-2C19 genotypes were 1.9 and 1.6 times higher respectively than the corresponding parameters for normal metabolising genotypes, whilst the C_{max} had increased by only 40%.	
ref. 35 SmPC Aciphex (rabeprazole sodium), USA, 18-07-23.	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 normal 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 normal 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. Drug interactions: Tacrolimus. Clinical Impact: Potentially increased exposure of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.	

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

Risk group	-

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+NM 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 NM, 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 NM and IM patients. A similar increase was not observed for pantoprazole. Sakurai et al., 2007 found no increase in the plasma concentration of lansoprazole from Day 1 to Day 5 following intravenous administration.

- Eradication of Hp
  Meta-analysis [Padol S et al. The effect of CYP2C19 polymorphisms on *H. pylori* eradication rate in dual and triple first-line PPI therapies: a meta-analysis. Am J Gastroenterol 2006;101:1467-75] examining the evidence supporting a relationship between the CYP2C19 genotype and eradication of *H. pylori* in primary care.
  Eradication percentages for the different PPIs (%) are in the order NM : IM: PM for omeprazole 62.9 : 76.7 : 92.7, for lansoprazole 74.4 : 82.9 : 87.5 and for rabeprazole 77.3 : 85.7 : 80.6.
  Authors' conclusion: "We suggest that the intermediate metabolizer term is accurate at the level of acid inhibition but does not translate into lower *H. pylori* eradication rates. Because only omeprazole is affected by CYP2C19 genotype status, it would be logical to increase the dose for this PPI to determine whether an increased dose could overcome the effect of the CYP2C19 genotypes on eradication rates. This can be done in a Caucasian population. (…) An alternate strategy to optimize *H. pylori* eradication would be to use first-line treatments that do not show CYP-2C19 polymorphism dependence on eradication rates. According to our meta-analysis, eradication treatments with lansoprazole and rabeprazole fulfil this criterion."
- In a response to the meta-analysis by Padol et al., Velthuyzen van Zanten S and Thompson K [Should the presence of polymorphisms of CYP2C19 enzymes influence the choice of the proton pump inhibitor for treatment of *Helicobacter pylori* infection? J Gastroenterol 2006;101:1476-78] made the following comment: the clearance of a PPI reduces with extended use, resulting in greater suppression of acid secretion. Therefore, results for a single dose cannot simply be extrapolated to long-term use.
- **Other guidelines**:
  - Lima JJ et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2C19 and proton pump inhibitor dosing. Clin Pharmacol Ther 2021;109:1417-23. PMID: 32770672.
    CPIC uses the same definition of UM as we do. However, CPIC uses a different definition for NM (only *1/*1). CPIC created a phenotype rapid metaboliser (RM) for *1/*17. In addition, whereas we do not distinguish between no function and decreased function alleles in our definitions of IM and PM, CPIC does. CPIC assigns genotypes with one reduced function allele and one normal or increased function allele and genotypes with two reduced function alleles to the phenotype 'likely IM'. In addition, CPIC assigns genotypes with one no function allele and one decreased function allele to the phenotype 'likely PM'. The summary below uses the KNMP definitions for NM, PM, IM and UM.
    CPIC indicates that there is less evidence linking CYP2C19 genotype with variability in plasma concentrations and effectiveness of second-generation PPIs, like rabeprazole, than of first-generation PPIs, both in terms of number of studies and strength of the association. CPIC indicates that the evidence associating CYP2C19 genotype with rabeprazole plasma concentrations, efficacy, and toxicity was graded as moderate (i.e. evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality or consistency of the individual studies, generalisability to routine practice, or the indirect nature of the evidence) or weak (i.e. evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information). However, in a supplementary table CPIC indicates that the level of evidence is high (i.e. evidence includes consistent results from well-designed, well-conducted studies) for the finding that CYP2C19 is not associated with H. pylori eradication rate when treated with rabeprazole when comparing PM vs IM vs NM. Finally, CPIC indicates that inconsistent findings regarding the effect of CYP2C19 genotype on the pharmacokinetics and therapeutic response to rabeprazole preclude making recommendations for this second-generation PPI (i.e., CPIC level C; no recommendation (i.e. there is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time)).
    On 9-8-2024, there was not a more recent version of the recommendations present on the CPIC-site.

Date of literature search: 29 July 2024.

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

bial 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.