CYP2C19: pantoprazole 2508 to 2510

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

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

Brief summary and justification of choices:

Pantoprazole is primarily metabolised by CYP2C19 and CYP3A4/5 to inactive metabolites. The extent and duration of effective acid inhibition by proton pump inhibitors is dependent on the AUC.

The literature shows that absent or reduced CYP2C19 activity (poor and intermediate metabolisers (PM and IM)) results in higher plasma concentrations and a higher pantoprazole AUC (Feldman 2022, Román 2014, Gawrońska-Szklarz 2012, Thacker 2011, Gawrońska-Szklarz 2010, and Kearns 2008) and an increase in CYP2C19 activity (ultra-rapid metaboliser (UM)) in a lower pantoprazole AUC (Gawrońska-Szklarz 2010).

IM and PM: With eradication of Helicobacter pylori, a favourable effect was found for IM (significant in 1 of the 6 studies and none of the two small meta-analyses) (Gawronska-Szklarz 2005) and for IM+PM (significant in 1 of the 2 studies) (Kurzawski 2006). There are no significant data for PM (6 studies and 2 small meta-analyses). An increased efficiency was found for treatment of gastroesophageal reflux disease in IM and PM (significant in both studies) (Sheu 2012 and Chen 2010). In addition, a significant reduction in the accuracy of the PPI test was found for PM, which points to improved effectiveness in reduction of GERD symptoms in patients with non-erosive oesophagitis (Tseng 2009). There are no studies investigating the influence of PM and IM on efficiency of treatment of peptic ulcer/bleeding. A better pH inhibition was found for IM and PM with gastroesophageal reflux disease (significant in 1 of the 2 studies for IM (Hunfeld 2010) and not-significant in the only study for PM) and for PM with bleeding peptic ulcer in case of once daily dosing (Oh 2007) (not significant with twice daily dosing and for IM). In studies that examined side effects, there were no serious side effects (Chang 2019, Ormeci 2016, and Hsu 2015).
As these gene-drug interactions have no negative effects, the KNMP Pharmacogenetics Working Group decided that no action is required (yes/no-interactions).

UM: No significant clinical results were found for UM (2 studies on eradication of Helicobacter pylori and 1 study investigating gastric acid inhibition in gastroesophageal reflux disease pstients) (Gawrońska-Szklarz 2010, Kurzawski 2006, and Deshpande 2016). However, a reduced therapeutic efficacy on reflux oesophagitis, eradication of Helicobacter pylori and peptic ulcer/bleeding was found for NM as compared to IM and PM. This effect of reduced effectiveness with an increase in CYP2C19 activity will apply to a greater extent to UM patients. For this reason, a dose increase is recommended (yes/yes-interaction).
There are few kinetic data for UM in comparison with NM (11 UM in 4 studies) (Feldman 2022, Deshpande 2016, Román 2014, and Gawrońska-Szklarz 2012) or PM (8 UM in 3 studies) (Feldman 2022, Deshpande 2016, and Gawrońska-Szklarz 2012). In addition, the calculated dose increase for UM compared to NM (weighted mean dose increase up to 149% of the normal dose (132-222%; median 146%) was much smaller than that for NM compared to PM. For this reason, the calculated dose increase was based only on the difference between NM and PM, so on the dose increase needed to achieve a similar exposure following oral or intravenous administration in NM patients as in 20 PM patients from 7 studies (Feldman 2022, Deshpande 2016, Gawrońska-Szklarz 2012, Thacker 2011, Choi 2009, Hunfeld 2008, and Kearns 2008). The weighted mean was a dose increase up to 498% of the normal dose (277-2443%; median 551%)). The KNMP Pharmacogenetics Working Group translated this to a figure of 500% to be achievable in practice. Because the recommended dose increase is large and relatively high doses are also less com-

mon for pantoprazole than for other PPIs, healthcare providers may be reluctant to follow the recommendation for a dose increase. For this reason, a switch to another PPI is mentioned as another option.

You can find a detailed overview of the observed kinetic and clinical effects in the background information text of the gene-drug interactions in the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

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

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

The clinical implication of the gene-drug interaction scores 1 out of the maximum of 10 points (with pre-emptive genotyping considered to be potentially beneficial for scores ranging from 0 to 2 points) (see also the clinical implication score tables at the end of this risk analysis):

Pantoprazole showed diminished efficacy in patients without genetically diminished CYP2C19 activity (normal metabolisers (NM) and ultra-rapid metabolisers (UM)). However, diminished efficacy has not been substantiated for UM compared to NM. In addition, this diminished efficacy does not have a high clinical impact (severity code B or C corresponding to CTCAE grade 1 or 2). For patients with genetically diminished CYP2C19 activity, no increase in an adverse event with severity code higher than C (corresponding to CTCAE grade 2) was found. This results in a score of 0 out of the maximum of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (only points for CTCAE grade ≥ 3).

The lack of a severe clinical effect also results in a score of 0 of the maximum of 3 points for the second and third criterion of the clinical implication score: the level of evidence supporting an associated clinical effect grade ≥ 3 and the number needed to genotype (NNG) in the Dutch population to prevent one clinical effect code ≥ D (grade ≥ 3).

The Summary of Product Characteristics (SmPC) does not mention the CYP2C19 UM phenotype, but mentions exposure in CYP2C19 PM to be many times higher than in CYP2C19 NM+IM. This results in 1 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (1 point for at least one genotype/phenotype being mentioned in the SmPC, but not mentioned as a contra-indication and no recommendation to genotype).

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

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

For the period after January 2010, references are listed based on the date of publication only. For the period before, GERD-references are listed first, followed by ulcer/bleeding-references, Hp-references, and kinetic references.

Source	Code	Effect	Comments
ref. 1, 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.	3	Meta-analysis of 3 controlled trials with a total of 602 patients (226 NM, 301 IM, and 75 PM) with H. pylori infection treated with triple therapy with pantoprazole. Treatment duration was 7 days. Pantoprazole doses in the studies were not mentioned. All studies in this meta-analysis were also included in this risk analysis separately (Lee 2014, Gawrońska-Szklarz 2010, and Oh 2009). None of the studies in this meta-analysis were included in the meta-analysis of Fu 2021. 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. Possible publication bias was analysed, but only for all studies (all PPIs), not for the subgroup of pantoprazole	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.'

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

IM: AA</td><td>studies.

Results:<table><tr><td colspan="2">H. pylori eradication rate compared to NM (eradication in 80.5% of patients):</td></tr><tr><td rowspan="2">PM</td><td>NS</td></tr><tr><td>The H. pylori eradication rate for PM was 85.3%.</td></tr><tr><td rowspan="2">IM</td><td>NS</td></tr><tr><td>The H. pylori eradication rate for IM was 77.1%.</td></tr><tr><td colspan="2">Heterogeneity between the studies was not significant for IM compared to NM and absent for PM compared to NM.</td></tr></table></td><td></td></tr>
<tr><td>ref. 2, kin
Feldman K et al.
Utility of the 13 C-pantoprazole breath test as a CYP2C19 phenotyping probe for children.
Clin Transl Sci 2022;15:1155-66.
PMID: 35099109.</td><td>4

UM: AA
IM: A

PM: AA

*1/*17: AA</td><td>61 children with or without gastroesophageal reflux disease received a single dose of ^{13}C-labelled pantoprazole 1.2 mg/kg lean body weight with a maximum of 100 mg. Mean age was 13.81 years (range 6.08-17.92 years). Children participated in a study on appropriate PPI dosing for obese children and mean weight was 61,71 kg (range 18,50-124,00 kg).
Plasma concentrations were determined until 8 hours after pantoprazole administration. Pantoprazole total area under the concentration-time curve (AUC_{tot}) was determined and corrected for dose in mg/kg total body weight.
Co-medication known to induce or inhibit CYP2C19 and concomitant proton pump inhibitor therapy were excluded.

Genotyping:
- 1x UM
- 46x NM
- 13x IM (10x *1/*2, 3x *2/*17)
- 1x PM

Results:<table><tr><td colspan="2">Dose-corrected AUC_{tot} compared to NM (AUC_{tot} = 9,27 µmol/L per mg/kg):</td></tr><tr><td>UM</td><td>x 0.45 (NS) (significance not determined)</td></tr><tr><td>*1/*2</td><td>x 1.95 (S)</td></tr><tr><td>*2/*17</td><td>x 1.12 (NS)</td></tr><tr><td>PM</td><td>x 24.43 (NS) (significance not determined)</td></tr><tr><td colspan="2">NOTE: Dosing was based on lean body weight, but dose correction on total body weight.</td></tr><tr><td colspan="2">NOTE: There was no significant difference in AUC_{tot} between *1/*1 and *1/*17.</td></tr></table>
NOTE: Genotyping was for *2 to *4, and *17. These are the most important alleles in this population from the USA. Only *2 and *17 were detected in this patient group.</td><td>Authors' conclusion: 'In addition to significantly increased plasma pantoprazole AUC_{tot} and significantly decreased pantoprazole CL/F, plasma ratios of pantoprazole to CYP2C19-mediated metabolites were significantly higher in NM versus IM.'

AUC versus NM:
UM: 45%
IM: 176%
PM: 2443%</td></tr>
<tr><td>ref. 3, 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 5 Asian studies (1 randomised controlled trial and 4 cohort studies) with a total of 786 patients (303 NM, 304 IM, and 179 PM) with H. pylori infection treated with triple or quadruple therapy. The pantoprazole dose used was 40 mg twice a day in all studies (during 1 week in 2 studies, during 10 days in 1 study, and during 2 weeks in 2 studies). 2 of the included studies with a total of 286 patients (102 NM, 119 IM, and 65 PM) used quadruple therapy. All included studies were assessed as low risk of bias using the Cochrane bias risk assessment tool (based on scoring low, uncertain or high risk of bias in 7 domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective</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. 3, continuation</td>
<td>IM: AA

PM: AA</td>
<td>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). The included randomised trial had a low risk of bias in 4 domains, an uncertain risk in 2 domains (allocation concealment and selective reporting), and a high risk in 1 domain (other bias). One of the four included cohort studies scored 8 points on the Newcastle-Ottawa Scale, one 7 points and the other two 6 points.
All three triple therapy studies included in the meta-analysis were also included in this risk analysis separately (Chang 2019, Ormeci 2016, and Kang 2008).
Meta-analyses were performed with a random-effects model, but prospective registration of the protocol was not mentioned. The search and selection strategy was transparent and the data extraction was standardised.
Possible publication bias was analysed only for all studies (all PPIs), not for the subgroup of pantoprazole 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 77.6% of patients):</td></tr>
<tr><td rowspan="2">IM</td><td>NS</td></tr>
<tr><td>The H. pylori eradication rate for IM was 80.6%.</td></tr>
<tr><td rowspan="2">PM</td><td>trend for a higher eradication rate (p = 0.088) (NS)</td></tr>
<tr><td>The H. pylori eradication rate for PM was 84.9%.</td></tr>
<tr><td colspan="2">NOTE: Of the two studies using triple instead of quadruple therapy, one was the only study showing a lower eradication for PM and one of the two studies showing a lower eradication rate for IM, while the other showed the one but strongest increase in eradication rate for PM and the strongest for IM.</td></tr>
<tr><td colspan="2">For both comparisons, there was no heterogeneity between the studies.</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>ref. 4, Hp
Chang YW et al. Clarithromycin resistance and female gender affect Helicobacter pylori eradication failure in chronic gastritis. Korean J Intern Med 2019;34:1022-9. PMID: 29898576.</td>
<td>3

PM: AA
IM:AA</td>
<td>190 H. pylori-positive patients with chronic gastritis were treated with triple therapy with pantoprazole 40 mg, amoxicillin 1000 mg and clarithromycin 500 mg twice daily for 1 week.
H. pylori status was determined 4 weeks after treatment. Antibiotics or PPIs in the 4 weeks prior to treatment were excluded. Other relevant co-medication was not excluded.
H. pylori was clarithromycin-resistant in 17.4% of patients.

Genotyping:
- 41x NM
- 75x IM
- 74x PM

Results:
<table>
<tr><td>H. pylori eradication rate for PM versus IM versus NM (value for NM: 63.4% of patients):</td></tr>
<tr><td>NS</td></tr>
<tr><td>The H. pylori eradication rates for PM and IM were 70.3% and 69.3% respectively.</td></tr>
<tr><td>Except for two patients who were not included in the study because they discontinued treatment due to severe adverse events, there were no severe adverse events.</td></tr>
</table>

NOTE: Genotyping was for *2 and *3. These are the most important gene variants in this Korean population.</td>
<td>Authors’ conclusion: ‘CYP2C19 genotypes were identified as follows: 75 poor metabolizers, 75 intermediate metabolizers, and 40 rapid metabolizers. Nonetheless, this polymorphism was not significantly associated with eradication failure.’</td>
</tr>
</table>

<table>
<tr>
<td>ref. 5, GERD
Deshpande N et al.
Rapid and ultra-rapid metabolizers with CYP2C19*17 polymorphism do not respond to standard therapy with proton pump inhibitors.
Meta Gene 2016;9:159-64.
PubMed PMID: 27419077.</td>
<td>4

PM: A
IM: AA
UM: AA
*1/*17: AA</td>
<td>9 healthy volunteers, selected for their CYP2C19 genotypes, received pantoprazole 40 mg once daily for 5 days.
Intragastric pH was determined in 6 patients before start of pantoprazole and 24 hours after the dose on day 5.
Relevant co-medication was not explicitly excluded, but volunteers were healthy.

Genotyping:
Kinetic study:
- 1x UM
- 1x *1/*17
- 2x (*1/*1+*2/*17+*3/*17)
- 2x IM (*1/*2+*1/*3)
- 3x PM

Clinical study:
- 1x UM
- 1x (*1/*1+*2/*17+*3/*17)
- 2x IM (*1/*2+*1/*3)
- 2x PM

Results:
<table>
<tr><td colspan="6">PM versus IM versus (*1/*1+*2/*17+*3/*17) versus *1/*17 versus UM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>*1/*17</td><td>UM</td><td>value for (*1/*1+*2/*17+*3/*17)</td></tr>
<tr><td>AUC at day 1</td><td>x 1.43</td><td>x 1.20</td><td>x 1.46</td><td>x 0.84</td><td rowspan="2">14.73 µg.hr/ml</td></tr>
<tr><td colspan="4">S for PM versus (*1/*1+*2/*17+*3/*17).
NS for the trend PM versus IM versus (*1/*1+*2/*17+*3/*17) versus *1/*17 versus UM.</td></tr>
<tr><td>AUC at day 5</td><td>x 4.11</td><td>x 2.29</td><td>x 0.86</td><td>x 0.68</td><td rowspan="2">10.59 µg.hr/ml</td></tr>
<tr><td colspan="4">S for PM versus (*1/*1+*2/*17+*3/*17).
NS for the trend PM versus IM versus (*1/*1+*2/*17+*3/*17) versus *1/*17 versus UM.</td></tr>
<tr><td>increase in intragastric pH</td><td>x 1.6</td><td>x 1.5</td><td></td><td>x -0.04</td><td>173%</td></tr>
<tr><td>intragastric pH at day 6 ≥ 4</td><td>yes</td><td>yes</td><td></td><td>no</td><td>yes</td></tr>
<tr><td>intragastric pH at day 6 ≥ 3</td><td>yes</td><td>yes</td><td></td><td>no</td><td>yes</td></tr>
<tr><td colspan="6">There was no significant difference in pharmacokinetic parameters between day 1 and day 5.</td></tr>
</table>
NOTE: Genotyping was for *2 to *10, *12 and *17. Only *2, *3 and *17 were detected in this Indian population.</td>
<td>Authors' conclusion: 'Interestingly, noteworthy differences could not be observed in the intra-gastric pH at baseline and on day 6 in response to administration of esomeprazole or pantoprazole in rapid and ultra-rapid metabolizers who are carriers of gain of function polymorphism CYP2C19*17.'

AUC versus (*1/*1+*2/*17+*3/*17):
PM: 277%
IM: 174%
UM: 76%</td>
</tr>
<tr>
<td>ref. 6, Hp
Ormeci A et al.
Effect of cytochrome P450 2C19 polymorphisms on the Helicobacter pylori eradication rate following two-week triple therapy with pantoprazole or rabeprazole.
Eur Rev Med Pharmacol Sci 2016;20:879-85.</td>
<td>3</td>
<td>104 patients with H. pylori infection, non-ulcer dyspepsia and endoscopic evidence of gastritis were treated with triple therapy with pantoprazole 40 mg, amoxicillin 1000 mg and clarithromycin 500 mg twice daily for 2 weeks.
H. pylori status was determined 2.5 months after treatment.
Acid-suppressants, antibiotics or anticoagulants in the 4 weeks prior to treatment were excluded. Other relevant co-medication was not excluded.
Although the prevalence of clarithromycin-resistant H. pylori in this area is higher than 20%, clarithromycin resistance was not excluded.

Genotyping:
- 81x NM</td>
<td>Authors' conclusion: 'We found that pantoprazole efficacy was not affected by CYP2C19 genotype polymorphism. However, further studies with a larger population are warranted to verify our findings.'</td>
</tr>
</table>

<table>
<tr>
<td>PubMed PMID: 27010145.

ref. 6, continuation</td>
<td>IM+PM: AA</td>
<td>- 22x IM
- 1x PM

Results:
<table>
<tr><td colspan="2">H. pylori eradication rate compared to NM (eradication in 69% of patients):</td></tr>
<tr><td>IM+PM</td><td>NS</td></tr>
<tr><td colspan="2">2.9% of the patients had an adverse event (diarrhoea, nausea or dizziness). There were no serious adverse events.</td></tr>
</table>
NOTE: Genotyping was for *2 and *3. Next to *17, these are the most important gene variants in this Turkish population.</td>
<td></td>
</tr>
<tr>
<td>ref. 7, Hp
Hsu PI et al.
A randomized controlled study comparing reverse hybrid therapy and standard triple therapy for Helicobacter pylori infection.
Medicine (Baltimore) 2015;94:e2104.
PubMed PMID: 26632893.</td>
<td>3

IM: AA
PM: AA</td>
<td>211 patients with H. pylori infection and peptic ulcer disease or gastritis were treated with triple therapy with pantoprazole 40 mg, amoxicillin 1000 mg and clarithromycin 500 mg twice daily for 12 days. After triple therapy, patients with peptic ulcer disease were treated with pantoprazole 40 mg once daily and patients with gastritis with antacids for 4 weeks.
H. pylori status was determined 6 weeks after treatment.
8% of the patients was clarithromycin resistant.
Antibiotics or bismuth in the 4 weeks prior to treatment were excluded. Other relevant co-medication was not excluded.
The associations with CYP2C19 genotype was assessed by univariate analysis.

Genotyping:
- 100x NM
- 81x IM
- 30x PM

Results:
<table>
<tr><td colspan="2">H. pylori eradication rate compared to NM (eradication in 90% 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>
<tr><td colspan="2">9.5% of the patients had an adverse event. 3 patients discontinued treatment due to an adverse event (1x diarrhoea, 1x dizziness, 1x skin rash).</td></tr>
</table>
NOTE: Genotyping was for *2 and *3. These are the most important gene variants in this Taiwanese population.</td>
<td>Authors' conclusion: 'CYP2C19 genotypes did not affect the eradication rates in both groups (reverse hybrid and standard triple group).'</td>
</tr>
<tr>
<td>ref. 8, Hp
Lee JY et al.
Factors affecting first-line triple therapy of Helicobacter pylori including CYP2C19 genotype and antibiotic resistance.
Dig Dis Sci 2014;59:1235-43.
PMID: 24599773.</td>
<td>3

PM: AA</td>
<td>271 patients were treated with triple therapy with pantoprazole 40 mg, amoxicillin 1000 mg and clarithromycin 500 mg twice daily for 1 week.
H. pylori status was determined 4 weeks after treatment.
Co-medication affecting CYP2C19 was not excluded.
H. pylori was clarithromycin-resistant in more than 23% of patients.

Genotyping:
- 119x NM
- 119x IM
- 33x PM

Results:
<table>
<tr><td colspan="2">H. pylori eradication rate compared to NM+IM (eradication in 78.6% of patients):</td></tr>
<tr><td rowspan="2">PM</td><td>trend for an increase (p = 0.096) (NS)</td></tr>
<tr><td>The H. pylori eradication rate for PM was 90.9%.</td></tr>
</table>
<table>
<tr><td>H. pylori eradication rate compared to NM (eradication in 82.4% of patients):</td></tr>
</table></td>
<td>Authors' conclusion: 'The eradication rates for the PM group were higher than those for the non-PM group with both regimens (esomeprazole and pantoprazole based triple therapy) but without statistically significant differences.'</td>
</tr>
</table>

<table>
<tr><td>ref. 8, continuation</td><td></td><td><table><tr><td rowspan="2">PM</td><td>x 1.10 (significance not determined)</td></tr><tr><td>The H. pylori eradication rate for PM was 90.9%.</td></tr><tr><td rowspan="2">IM</td><td>x 0.91 (significance not determined)</td></tr><tr><td>The H. pylori eradication rate for IM was 74.8%.</td></tr></table>
NOTE: Genotyping was for *2 and *3. These are the most important gene variants in this Korean population.</td><td></td></tr>
<tr><td>ref. 9, kin
Román M et al.
Evaluation of the relationship between polymorphisms in CYP2C19 and the pharmacokinetics of omeprazole, pantoprazole and rabeprazole.
Pharmacogenomics 2014;15:1893-901.
PubMed PMID: 25495411.</td><td>3

IM: A
*1/*17: AA
UM: AA</td><td>77 healthy volunteers received a single dose of 40 mg pantoprazole on two separate occasions.
Relevant co-medication was not explicitly excluded, but volunteers were healthy.

Genotyping:
- 3x UM
- 27x *1/*17
- 32x *1/*1
- 1x *2/*17
- 14x *1/*2

Results:<table><tr><td colspan="2">AUC compared to *1/*1 (5.67 µg.hr/ml):</td></tr><tr><td>*1/*2</td><td>x 1.86 (S)</td></tr><tr><td>*2/*17</td><td>x 0.94</td></tr><tr><td>*1/*17</td><td>x 1.00 (NS)</td></tr><tr><td>UM</td><td>x 0.64 (NS)</td></tr><tr><td colspan="2">Multiple regression analysis confirmed the significant effect of being a *2 carrier and the absence of a significant effect of being a *17 carrier.</td></tr></table>
NOTE: Genotyping was for *2, *3 and *17. *3 was not found in this Spanish population.</td><td>Authors’ conclusion: ‘CYP2C19*2 is associated with decreased clearance of all the PPIs, that could be associated with higher drug efficacy. CYP2C19*17 could increase clearance of these drugs, although the effect seems small.’

AUC versus NM:
IM: 181%
UM: 64%</td></tr>
<tr><td>ref. 10, kin
Gawrońska-Szklarz B et al.
CYP2C19 polymorphism affects single-dose pharmacokinetics of oral pantoprazole in healthy volunteers.
Eur J Clin Pharmacol 2012;68:1267-74.
PubMed PMID: 22418828.</td><td>3

PM: AA
IM: A
*1/*17: AA
UM: AA</td><td>32 healthy volunteers, selected for their CYP2C19 genotypes, received a single dose of 40 mg pantoprazole.
Relevant co-medication was not explicitly excluded, but volunteers were healthy.

Genotyping:
- 6x UM
- 6x *1/*17
- 6x *1/*1
- 6x *2/*17
- 6x *1/*2
- 2x PM

Results:<table><tr><td colspan="2">AUC compared to *1/*1 (3.00 µg.hr/ml):</td></tr><tr><td>PM</td><td>x 5.06 (NS)</td></tr><tr><td>*1/*2</td><td>x 1.46 (S)</td></tr><tr><td>*2/*17</td><td>x 1.19 (NS)</td></tr><tr><td>*1/*17</td><td>x 0.71 (NS)</td></tr><tr><td>UM</td><td>x 0.62 (NS)</td></tr><tr><td colspan="2">Population modelling confirmed a strong influence of *1/*2, *2/*2 and *17/*17 genotypes on the pharmacokinetics of pantoprazole.</td></tr><tr><td colspan="2">In a group of 120 not selected volunteers, the authors found a ratio of 1:1 for the frequencies of *1/*1 and *1/*17 and a ratio of 5:4 for the frequencies of *1/*2 and *2/*17.</td></tr></table>
NOTE: Genotyping was for *2 and *17. These are the most important gene variants in this Polish population.</td><td>Authors’ conclusion: ‘These data suggest that CYP2C19 polymorphism is an important determinant of pantoprazole pharmacokinetics.’

AUC versus NM:
PM: 592%
IM: 157%
UM: 73%</td></tr>
<tr><td>ref. 11, GERD
Sheu BS et al.
CYP2C19 genoty-</td><td>3</td><td>200 patients, who achieved complete healing of severe reflux esophagitis (Los Angeles grade C or D) and were free of reflux related symptoms after pantoprazole 40 mg/day for</td><td>Authors’ conclusion: ‘For reflux esophagitis Los Angeles</td></tr>
</table>

<table>
<tr>
<td>pes determine the efficacy of on-demand therapy of pantoprazole for reflux esophagitis as Los-Angeles grades C and D.
J Gastroenterol Hepatol 2012;27:104-9.
PubMed PMID: 21777277.

ref. 11, continuation</td>
<td>PM: AA#
IM: AA#</td>
<td>6 months, were treated with on-demand therapy with 40 mg pantoprazole once daily for 1 year. 50% of the patients was infected with Helicobacter pylori. Patients received 90 tablets of pantoprazole 40 mg every 3 months.
Failure of on-demand therapy was defined as either obvious symptoms to shift from on-demand therapy back to continuous proton pump inhibitor usage for at least 7 days, or an unscheduled visit to load additional proton pump inhibitor, or an unscheduled endoscopy to confirm a progression of erosive esophagitis, or loss to follow-up.
Complete healing was defined as complete healing of the esophageal ulcer into the scar stage and total regression of erosive reflux esophagitis.
Patients were excluded from further participation in the study in case of failure of on-demand therapy, occurrence of bleeding or esophageal strictures or requirement of endoscopic biopsy to check the risk of malignancy.
Use of oestrogens, progestins, anti-obesity drugs, steroids and NSAIDs was excluded. Other relevant co-medication was not excluded.

Genotyping:
- 51x NM
- 108x IM
- 41x PM

Results:
<table>
<tr><td colspan="5">PM versus IM versus NM:</td></tr>
<tr><td colspan="2"></td><td>PM</td><td>IM</td><td>value for NM</td></tr>
<tr><td colspan="2">% of patients with successful therapy</td><td>x 1.6 (S)</td><td>x 1.5 (S)</td><td>51%</td></tr>
<tr><td rowspan="4">% of patients with therapy failure</td><td>month 1-3</td><td colspan="2">NS for PM versus IM versus NM</td><td>21.6%</td></tr>
<tr><td rowspan="2">month 4-6</td><td>x 0.22</td><td>x 0.46</td><td rowspan="2">25%</td></tr>
<tr><td colspan="2">S for PM versus IM versus NM</td></tr>
<tr><td rowspan="2">month 7-9</td><td>x 0</td><td>x 0.36</td><td rowspan="2">13.3%</td></tr>
<tr><td colspan="2">S for PM versus IM versus NM</td></tr>
<tr><td>month 9-12</td><td colspan="2">NS, trend for PM versus IM versus NM (p = 0.054)</td><td>7.7%</td></tr>
<tr><td colspan="2" rowspan="2">tablets used per month by patients with successful therapy</td><td>x 0.62</td><td>x 0.88</td><td rowspan="2">18.6</td></tr>
<tr><td colspan="2">S for PM versus IM versus NM</td></tr>
<tr><td rowspan="8">tablets used per month by patients not failing therapy in the indicated period</td><td rowspan="2">month 1-3</td><td>x 0.89</td><td>x 0.94</td><td rowspan="2">20.1</td></tr>
<tr><td colspan="2">S for PM versus IM versus NM</td></tr>
<tr><td rowspan="2">month 4-6</td><td>x 0.71</td><td>x 0.96</td><td rowspan="2">18.1</td></tr>
<tr><td colspan="2">S for PM versus IM versus NM</td></tr>
<tr><td rowspan="2">month 7-9</td><td>x 0.83</td><td>x 1.13</td><td rowspan="2">13.4</td></tr>
<tr><td colspan="2">S for PM versus IM versus NM</td></tr>
<tr><td rowspan="2">month 9-12</td><td>x 0.70</td><td>x 0.97</td><td rowspan="2">13.6</td></tr>
<tr><td colspan="2">S for PM versus IM versus NM</td></tr>
<tr><td colspan="2">% of complete healing in patients who did not fail therapy and completed follow-up</td><td colspan="2">NS for PM versus IM versus NM</td><td>88.5%</td></tr>
<tr><td colspan="5">Univariate analysis and multivariate logistic regression</td></tr>
</table>
</td>
<td>grade C or D with complete healing after continuous pantoprazole, the successful shift to on-demand therapy is determined by the CYP2C19 genotypes of the patients.’</td>
</tr>
</table>

<table>
<tr><td>ref. 11, continuation</td><td></td><td>confirmed NM to be an independent risk factor for therapy failure (OR = 3.41; 95% CI: 1.76-6.61) (S).

NOTE: Genotyping was for *2 and *3. These are the most important gene variants in this Taiwanese population.</td><td></td></tr>
<tr><td>ref. 12, kin
Thacker DL et al. Stereoselective pharmacokinetics of stable isotope (+/-)-[^{13}C]-pantoprazole: Implications for a rapid screening phenotype test of CYP2C19 activity. Chirality 2011;23:904-9. PubMed PMID: 21935988.</td><td>3

PM: A
IM: AA</td><td>24 healthy volunteers received a single dose of 100 mg [^{13}C]-pantoprazole sodium sesquihydrate with 2.1 g sodium bicarbonate.
Smoking and oral contraceptives were excluded, as was use of pantoprazole or sodium bicarbonate in the month preceding the study, Subjects were asked to refrain from taking any prescription, over-the-counter, or herbal medications and from alcohol consumption.

Genotyping:
- 10x NM
- 10x IM
- 4x PM

Results:
AUC compared to NM:
<table><tr><td></td><td>PM</td><td>IM</td><td>value for NM (µg. hr/ml)</td></tr><tr><td>(-)-pantoprazole</td><td>x 1.98 (S)</td><td>x 1.58 (NS)</td><td>4.31</td></tr><tr><td>(+)-pantoprazole</td><td>x 10.13 (S)</td><td>x 1.81 (NS)</td><td>2.90</td></tr><tr><td>(±)-pantoprazole</td><td>x 5.26 (S)</td><td>x 1.67 (NS)</td><td>7.21</td></tr><tr><td colspan="4">All differences were significant for PM versus IM versus NM (S).</td></tr></table>
NOTE: Genotyping was for *2, *3 and *17. These are the most important gene variants in this population of Asian origin.</td><td>Authors’ conclusion: ‘The AUC$_{(0-\infty)}$ of (+)-[^{13}C]-pantoprazole in PM was 10.1- and 5.6- fold higher that NM and IM of CYP-2C19 respectively. The AUC$_{(0-\infty)}$ of (−)-[^{13}C]-pantoprazole only significantly differed between PMs and NMs (1.98-fold).’

AUC versus NM:
PM: 526%
IM: 167%</td></tr>
<tr><td>ref. 13, GERD
Chen WY et al. Double-dosed pantoprazole accelerates the sustained symptomatic response in overweight and obese patients with reflux esophagitis in Los Angeles grades A and B. Am J Gastroenterol 2010;105:1046-52. PubMed PMID: 19904250.</td><td>3

PM: AA#
IM: AA#</td><td>200 overweight or obese patients (body mass index ≥ 25) with mild gastroesophageal reflux disease (Los Angeles grade A or B) were treated with either pantoprazole 40 mg once daily (n = 100) or pantoprazole 40 mg twice daily (n = 100) for 8 weeks. 53% of the patients was infected with Helicobacter pylori.
Patients recorded their daily gastroesophageal reflux symptoms (with a 4-point scale for each symptom). A sustained symptomatic response was defined as the absence of acid regurgitation and heartburn for the last 7 days.
Use of antisecretory agents in the preceding 4 weeks was excluded, as was use of anti-obesity medication. Other relevant co-medication was not excluded.

Genotyping:
- 81x NM
- 86x IM
- 33x PM

Results:
% of patients with sustained symptomatic response for PM versus IM versus NM:
<table><tr><td colspan="2"></td><td>PM</td><td>IM</td><td>value for NM</td></tr><tr><td rowspan="4">pantoprazole 40 mg once daily</td><td rowspan="2">after 2 weeks</td><td>x 8.7</td><td>x 3.2</td><td rowspan="2">7.9%</td></tr><tr><td colspan="2">S for PM versus IM versus NM</td></tr><tr><td rowspan="2">after 4 weeks</td><td>x 3.7</td><td>x 1.8</td><td rowspan="2">23.7%</td></tr><tr><td colspan="2">S for PM versus IM versus NM</td></tr></table></td><td>Authors’ conclusion: ‘For reflux esophagitis of Los Angeles grade A or B in overweight and obese patients, double-dosed pantoprazole effectively accelerates the sustained symptomatic response, especially for those with CYP-2C19 genotypes as IM or NM.’</td></tr>
</table>

<table>
<tr>
<td>ref. 13, continuation</td>
<td></td>
<td>
<table>
<tr><td></td><td>after 8 weeks</td><td>x 1.5</td><td>x 1.1</td><td>68.4%</td></tr>
<tr><td></td><td></td><td colspan="2">S for PM versus IM versus NM</td><td></td></tr>
<tr><td rowspan="4">pantoprazole 40 mg twice daily</td><td>after 2 weeks</td><td>x 7.8</td><td>x 4.7</td><td>7.5%</td></tr>
<tr><td></td><td colspan="2">S for PM versus IM versus NM</td><td></td></tr>
<tr><td>after 4 weeks</td><td colspan="2">NS for PM versus IM versus NM</td><td>55%</td></tr>
<tr><td>after 8 weeks</td><td colspan="2">NS, trend for PM versus IM versus NM, p = 0.052</td><td>82.1%</td></tr>
</table>
<table>
<tr><td colspan="4">% of patients with sustained symptomatic response for pantoprazole 40 mg twice daily versus once daily:</td></tr>
<tr><td colspan="2"></td><td></td><td>value for 40 mg once daily</td></tr>
<tr><td rowspan="4">NM</td><td>after 2 weeks</td><td>NS</td><td>7.9%</td></tr>
<tr><td>after 4 weeks</td><td>x 2.3 (S)</td><td>23.7%</td></tr>
<tr><td>after 8 weeks</td><td>NS</td><td>68.4%</td></tr>
<tr><td>cumulative over 8 weeks</td><td>S</td><td></td></tr>
<tr><td rowspan="4">IM</td><td>after 2 weeks</td><td>NS</td><td>25.6%</td></tr>
<tr><td>after 4 weeks</td><td>x 1.6 (S)</td><td>41.9%</td></tr>
<tr><td>after 8 weeks</td><td>x 1.3 (S)</td><td>73.7%</td></tr>
<tr><td>cumulative over 8 weeks</td><td>S</td><td></td></tr>
<tr><td rowspan="4">PM</td><td>after 2 weeks</td><td>NS</td><td>68.8%</td></tr>
<tr><td>after 4 weeks</td><td>NS</td><td>87.5%</td></tr>
<tr><td>after 8 weeks</td><td>NS</td><td>100%</td></tr>
<tr><td>cumulative over 8 weeks</td><td>NS</td><td></td></tr>
<tr><td colspan="4">After 8 weeks, the percentage of patients with a sustained symptomatic response was numerically higher for PM on 40 mg once daily (100%) than for IM and NM on 40 mg twice daily (respectively 94.9% and 82.1%) (NS, trend).</td></tr>
</table>
NOTE: Genotyping was for *2 and *3. These are the most important gene variants in this Taiwanese population.
</td>
<td></td>
</tr>
<tr>
<td>ref. 14, Hp
Gawrońska-Szklarz B et al.
Effects of CYP2C19, MDR1, and interleukin 1-B gene variants on the eradication rate of Helicobacter pylori infection by triple therapy with pantoprazole, amoxicillin, and metronidazole.
Eur J Clin Pharmacol 2010;66:681-7.
PubMed PMID: 20376628.</td>
<td>3</td>
<td>139 patients with H. pylori infection and peptic ulcer disease were treated with triple therapy with pantoprazole 40 mg, amoxicillin 1000 mg and metronidazole 500 mg twice daily for 1 week. After triple therapy, patients were treated with pantoprazole 40 mg once daily for 5 weeks.
H. pylori status and pantoprazole plasma concentration were determined 6 weeks after start of treatment. Eradication of H. pylori was successful in 74% of patients.
Although the prevalence of metronidazole-resistant H. pylori in this area is 30-40%, metronidazole resistance was not excluded.
Relevant co-medication was not excluded.
The study had a power of more than 80% to detect a higher than 14% difference in allele frequency between the groups stratified according to treatment outcome (assuming a treatment success rate of 75% and minor allele frequency of 15%).

Genotyping:
clinical study:
- 12x UM
- 47x *1/*17
- 47x *1/*1
- 7x *2/*17
- 24x *1/*2
- 2x PM
kinetic study:
- 3x UM
- 6x *1/*17
- 6x *1/*1
- 3x *2/*17
- 7x *1/*2</td>
<td>Authors’ conclusion: ‘The results suggest that the CYP2C19 genotype contrary to MDR1 and IL-1B genotypes may have an impact on the efficacy of H. pylori eradication in peptic ulcer patients treated with pantoprazole in Polish Caucasian peptic ulcer patients administered pantoprazole, amoxicillin, and metronidazole.’</td>
</tr>
</table>

<table>
<tr>
<td>ref. 14, continuation</td>
<td>UM: A
IM: A
PM: A</td>
<td>Results:
PM versus *1/*2 versus 2/*17 versus *1/*1 versus *1/*17 versus UM:
<table>
<tr><td></td><td>PM</td><td>*1/*2</td><td>*2/*17</td><td>*1/*17</td><td>UM</td><td>value for *1/*1</td></tr>
<tr><td>% of patients with succesful eradication</td><td colspan="5">NS for the trend PM versus *1/*2 versus 2/*17 versus *1/*1 versus *1/*17 versus UM.
NS for the trend PM versus IM versus (NM+UM).
There was a trend for a higher frequency of the *2-allele in patients with successful eradication compared to patients with failure of eradication (NS, p = 0.10).
There was a trend for CYP2C19 as a predictive factor for treatment success in univariate analysis (p = 0.10), but not in multivariate analysis (p = 0.20) (NS).</td><td>68%</td></tr>
<tr><td>plasma concentration 3 hr after dosing</td><td></td><td>x 1.9</td><td>x 0.8</td><td>x 1.4</td><td>x 0.5</td><td>1.18 µg/ml</td></tr>
<tr><td></td><td colspan="5">S for *1/*2 versus 2/*17 versus *1/*1 versus *1/*17 versus UM.</td><td></td></tr>
</table>
NOTE: Genotyping was for *2, *3 and *17. *3 was not found in this Polish population.</td>
<td></td>
</tr>
<tr>
<td>ref. 15 - GERD
Hunfeld NG et al.
A comparison of the acid-inhibitory effects of esomeprazole and pantoprazole in relation to pharmacokinetics and CYP2C19 polymorphism.
Aliment Pharmacol Ther 2010;31:150-9.</td>
<td>4

IM: AA#

*17: AA</td>
<td>18 healthy volunteers (7x *1/*1, 7x *1/*2, 2x *1/*17, 2x *2/*17) received panto 40 mg/day 1x daily for 5 days, no relevant co-medication;

*1/*1 versus *1/*2:
- smaller % time with intragastric pH > 4 for 24 hours on days 1 and 5 (S)
- lower median intragastric pH on days 1 and 5 (S)
- lower AUC on day 1 (3.82 : 7.95 mg.h/L (S)) and on day 5 (4.12 : 8.90 mg.h/L (S))
The AUC did not differ between day 1 and day 5 (NS).

*1 versus *17:
- % time with intragastric pH > 4 for 24 hours on day 1:
- approximately 25 : 21 (NS) for *1/*1 versus *1/*17
- approximately 40 : 27 (NS) for *1/*2 versus *2/*17

Note: Genotyping was performed for *2 to *6 and *17.</td>
<td>Authors’ conclusion: “In contrast to esomeprazole, pantoprazole metabolism is influenced by CYP2C19 polymorphism.”

AUC versus *1/*1:
IM: 212%</td>
</tr>
<tr>
<td>ref. 16 - GERD
Tseng PH et al.
A comparative study of proton-pump inhibitor tests for Chinese reflux patients in relation to the CYP2C19 genotypes.
J Clin Gastroenterol 2009;43:920-5.</td>
<td>3

PM: AA#</td>
<td>The aim of this study was to distinguish - based on the reduction in GERD symptoms by pantoprazole - between erosive GERD (usually reduced pH) and non-erosive GERD (less commonly associated with reduced oesophageal pH).
87 patients with erosive oesophagitis (n=41) or non-erosive oesophagitis (n=36), 70x (NM+IM), 8x PM, received pantoprazole 40 mg 2x daily for 2 weeks, co-medication unknown;

(NM + IM) versus PM:
- accuracy of the PPI test (%): 74.3 : 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.</td>
<td>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.”</td>
</tr>
</table>

ref. 16, continuation		Note: Genotyping was performed for *2 and *3.	
ref 17 - GERD Hunfeld NG et al. Effect of CYP2C19 *2 and *17 mutations on pharmacodynamics and kinetics of proton pump inhibitors in Caucasians. Br J Clin Pharmacol 2008;65:752-60.	4 *1/*17: A IM: AA PM: AA	16 H. pylori-negative healthy volunteers (6x *1/*1, 6x *1/*17, 1x *2/*17, 2x *1/*2, 1x *2/*2) received pantoprazole 40 mg/day for 6 days. *1/*17 versus *1/*1: - no significant effect on the percentage of time with intragastric pH > 4 for 24 hours on Days 1 and 6 - pantoprazole increased the percentage of time with intragastric pH > 4 on Day 1 significantly for *1/*1, but not for *1/*17 - non-significant reduction in AUC on Days 1 and 6 AUC ratio for *2/*2 versus *1/*2 versus *2/*17 versus *1/*1 versus *1/*17: - Day 1: 3.0 : 3.6 : 1.4 : 1 : 0.75 (value for *1/*1 = 4.56 µg.h/ml) (NS) - Day 6: 4.9 : 4.2 : 1.4 : 1 : 0.79 (value for *1/*1 = 4.21 µg.h/ml) (NS) Note: Genotyping was performed for *2 to *6 and *17.	Authors' conclusion: "This study showed that the acid-inhibitory effects of pantoprazole in Caucasians were influenced by CYP2C19 status. Pantoprazole 40 mg provided significant acid-inhibition in *1/*1 but not in *1/*17 subjects after a single dose." AUC versus NM: IM: 346% PM: 442%

ref. 18 - ulcers/ bleeding
Choi KD et al.
Optimal dose of intravenous pantoprazole in patients with peptic ulcer bleeding requiring endoscopic hemostasis in Korea.
J Gastroenterol Hepatol 2009;24:1617-24.
	3
	
	IM: AA
	
	PM: AA
		Patients with bleeding benign peptic ulcers, 38-60% used NSAIDs or acetylsalicylic acid, other co-medication unknown.
		19 patients (5x NM, 10x IM, 4x PM, 58% Hp-positive) received a single dose of pantoprazole 80 mg I.V., followed by pantoprazole 8 mg/h I.V. for 3 days.
		21 patients (5x NM, 16x IM, 71% Hp-positive) received a single dose of pantoprazole 40 mg I.V., followed by pantoprazole 4 mg/h I.V. for 3 days.
		21 patients (8x NM, 11x IM, 2x PM, 86% Hp-positive) received pantoprazole 40 mg 1x daily I.V. for 3 days.
		
		NM versus IM:
		- pantoprazole 80 mg, 8 mg/h:
		  - % patients with intragastric pH > 6 for > 60% of the time: 50.0 : 66.7 (NS)
		- pantoprazole 40 mg, 4 mg/h:
		  - % patients with intragastric pH > 6 for > 60% of the time: 100 : 69.2 (NS)
		  - clearance (L/h): 4.73 : 4.02 (NS)
		- pantoprazole 40 mg 1x daily:
		  - % patients with intragastric pH > 6 for > 60% of the time: 20.0 : 16.7 (NS)
		
		NM versus IM versus PM:
		- pantoprazole 80 mg, 8 mg/h:
		  - clearance (L/h): 4.18 : 4.70 (NS) : 1.17 (NS)
		- pantoprazole 40 mg 1x daily:
		  - clearance (L/h): 8.23 : 3.00 (NS) : 0.85 (NS)
		
		Note: Genotyping was performed for *2 and *3.
			Clearance versus NM:
			40 mg 1x daily:
			IM: 36%
			PM: 10%
			
			80 mg, 8 mg/h:
			IM: 112%
			PM: 28%

ref. 19 - ulcers/ bleeding Oh JH et al. Low-dose intravenous pantoprazole for optimal inhibition of gastric acid in Korean patients. J Gastroenterol	3	Patients with bleeding peptic ulcers following successful endoscopic treatment (n=29) or with endoscopic mucosa resection for gastric neoplasmata (n=23), PPIs and H2-receptor antagonists were excluded, other co-medication unknown. 24 patients (10x NM, 9x IM, 5x PM, 63% Hp-positive) received pantoprazole 40 mg 1x daily I.V. for 3 days. 28 patients (10x NM, 15x IM, 3x PM, 75% Hp-positive) recei-	Authors' conclusion: "In the pantoprazole q.d. group, patients with the PM genotype displayed greater acid inhibition than those with a IM or NM genotype. In the pantoprazole b.i.d.

Hepatol 2007;22:1429-34.
 	
ref. 19, continuation
	IM: AA
	PM: AA[#]
	
	PM: AA
		ved pantoprazole 40 mg 2x daily I.V. for 3 days.
		
		NM versus IM versus PM:
		- pantoprazole 40 mg 1x daily:
		  - median intragastric pH: 4.6 : 4.8 (NS) : 7.0 (S)
		  - % time pH > 6.0: 49.6 : 50.7 (NS) : 94.9 (S)
		  - % time pH > 4.0: 64.2 : 64.7 (NS) : 99.7 (S)
		  - % patients with median 24-hour pH <6.0: 50 : 56 (NS) : 0 (NS)
		- pantoprazole 40 mg 2x daily:
		  - median intragastric pH: 6.3 : 6.7 (NS) : 6.3 (NS)
		  - % time pH > 6.0: 72.2 : 81.5 (NS) : 70.6 (NS)
		  - % time pH > 4.0: 84.3 : 93.4 (NS) : 98.7 (NS)
		  - % patients with median 24-hour pH <6.0: 20 : 7 (NS) : 0 (NS)
		
		Note: Genotyping was performed for *2 and *3.
			group, however, the group effectively raised pH without significant differences in gastric acid inhibition between patients with PM and those with IM or NM genotype."

ref. 20 - Hp Oh JH et al. Effects of CYP2C19 and MDR1 genotype on the eradication rate of Helicobacter pylori infection by triple therapy with pantoprazole, amoxycillin and clarithromycin. J Gastroenterol Hepatol 2009;24:294-8.	3 IM: AA PM: AA	210 patients who had not previously received Hp eradication treatment (60x NM, 111x IM, 39x PM, approx. 75% clari-susceptible Hp) received 2x daily panto 40 mg + amoxi 1000 mg + clari 500 mg for 1 week; steroids, NSAIDs, PPIs, H2-receptor antagonists and antibiotics were excluded, other co-medication unknown; NM versus IM versus PM: - eradication %: 86.7 : 81.1 (NS) : 82.1 (NS) - multivariate analysis showed no effect of the CYP2C19 genotype on the eradication % NM versus PM: - eradication % for clari-resistant Hp: 28 : 75 (NS) Note: Genotyping was performed for *2 and *3.	Authors' conclusion: "The eradication rates of H. pylori by pantoprazole, amoxicillin and clarithromycin were not significantly different among the CYP-2C19 and MDR1 genotypes."
ref. 21 - Hp Kang JM et al. Effect of the CYP-2C19 polymorphism on the eradication rate of Helicobacter pylori infection by 7-day triple therapy with regular proton pump inhibitor dosage. J Gastroenterol Hepatol 2008;23:1287-91.	3 IM: AA PM: AA	190 patients (79x NM, 88x IM (*1/*2 of *1/*3), 23x PM (*2/*2 of *2/*3), 87% clari-susceptible Hp) received 2x daily panto 40 mg + amoxi 1000 mg + clari 500 mg for 1 week; steroids, NSAIDs, PPIs and antibiotics were excluded, other co-medication unknown; NM versus IM versus PM: - eradication %: 82.3 : 79.5 (NS) : 95.7 (NS) Note: Genotyping was performed for *2 and *3.	Authors' conclusion: "The results of this study suggest that the CYP2C19 genotype status may play a role in the H. pylori eradication rate in patients receiving pantoprazole or esomeprazole-based triple therapy."
ref. 22 - Hp Kurzawski M et al. Effect of CYP2C19 *17 gene variant on Helicobacter pylori eradication in peptic ulcer patients. Eur J Clin Pharmacol 2006;62:877-80.	3 IM+PM: AA[#] UM: AA	125 patients with peptic ulcers (44x *1/*1, 45x *1/*17, 7x *2/*17, 8x *17/*17, 20x *1/*2, 1x *2/*2) received 2x daily panto 40 mg + amoxi 1000 mg + metro 500 mg for 1 week, followed by panto 40 mg/day for 4 weeks for eradication of H. pylori. *1/*1 versus *2/*17 versus *1/*2 versus *2/*2: - eradication %: 52.3 : 100 (S) : 75 (NS) : 100 (NS) *1/*1 versus (IM + PM): - OR for eradication of Hp: 1.0 : 4.20 (95% CI 1.35-13.05) *1/*1 versus *1/*17 versus *17/*17: - eradication %: 52.3 : 60.0 (NS) : 62.5 (NS)	Authors' conclusion: "Our results suggest that, contrary to CYP2C19*2, CYP-2C19*17 allele has no impact on efficacy of H. pylori eradication in peptic ulcer patients treated with pantoprazole."

<table>
<tr><td></td><td></td><td>Note: Genotyping was performed for *2, *3 and *17.</td><td></td></tr>
<tr><td>ref. 23 - Hp
Gawronska-Szklarz B et al.
Effect of CYP2C19 and MDR1 polymorphisms on cure rate in patients with acid-related disorders with Helicobacter pylori infection.
Eur J Clin Pharmacol
2005;61:375-9.</td><td>3

IM: AA#</td><td>70 patients (56x NM, 14x IM (*1/*2)) received 2x daily ome 20 mg + amoxi 1000 mg + clari 500 mg (n=14) or panto 40 mg + amoxi 1000 mg + metro 500 mg (n=56) for 1 week; co-medication unknown;

- frequency of NM in group with eradication after treatment is significantly lower than in group without eradication (67.6% versus 91.7%).
- frequency of IM in group with eradication is significantly higher than in group without eradication (32.4% versus 8.3%).

Note: the results were not broken down for ome and panto
Note: apart from CYP2C19 genotype, panto/amoxi/metro regimen and genotype for MDR1 also appear to be associated with successful eradication.

Note: Genotyping was performed for *2 and *3.</td><td></td></tr>
<tr><td>ref. 24, kin
Kearns GL et al.
Single-dose pharmacokinetics of oral and intravenous pantoprazole in children and adolescents.
J Clin Pharmacol
2008;48:1356-65.
PubMed PMID: 18664620.</td><td>3

PM: AA
IM: A</td><td>24 children of 5 to 16 years old received a single oral dose of either 20 or 40 mg pantoprazole (both n = 12).
Co-medication was excluded.

Genotyping:
- 16x NM
- 5x IM
- 3x PM

Results:
<table><tr><td colspan="2">Dose- and weight-corrected AUC compared to NM (3.7 µg.hr.kg/ml.mg):</td></tr><tr><td>PM</td><td>x 12.30 (NS)</td></tr><tr><td>IM</td><td>x 1.38 (S)</td></tr><tr><td colspan="2">The authors did not find an influence of age on clearance (from 2 years on, including no difference in clearance between children and adults).</td></tr></table>
NOTE: Genotyping was for *2 to *5. If none of these gene variants was found or if genotype/phenotype discordance was observed, also *6 to *8 were genotyped. Next to *17, *2 to *8 are the most important gene variants in this American population.</td><td>Authors’ conclusion: “Statistically significant differences were observed for dose-normalized pantoprazole area under the plasma concentration-time curve when compared between CYP-2C19 normal metabolizers with 1 versus 2 functional alleles.”

AUC versus NM:
IM: 138%
PM: 1230%</td></tr>
<tr><td>ref. 25
SmPC Pantozol (pantoprazole) 26-04-23.</td><td>0

PM: A</td><td><u>Pharmacokinetics</u>:
Poor metabolisers
Approximately 3% of the European population lacks a functional CYP2C19 enzyme (CYP2C19 poor metabolisers). Most probably, the metabolism of pantoprazole is catalyzed mainly by CYP3A4 in these patients. After administration of a single dose of 40 mg pantoprazole, the mean area under the plasmaconcentration-time curve was approximately 6-fold higher in poor metabolisers than in persons with a functional CYP2C19 enzyme (extensive metabolisers). The mean peak plasma concentrations were increased with approximately 60%. These findings do not have implications for the pantoprazole dose.</td><td>AUC versus NM+IM:
PM: 600%</td></tr>
<tr><td>ref. 26
SmPC Protonix (pantoprazole sodium), USA, 18-07-23.</td><td>0</td><td><u>Pharmacogenomics</u>:
CYP2C19 displays a known genetic polymorphism due to its deficiency in some subpopulations (e.g., approximately 3% of Caucasians and African-Americans and 17% to 23% of Asians are poor metabolizers). Although these subpopulations of pantoprazole poor metabolizers have elimination half-life values of 3.5 to 10.0 hours in adults, they still have</td><td></td></tr>
</table>

ref. 26, continuation	PM: A	minimal accumulation (≤ 23%) with once-daily dosing. For adult patients who are CYP2C19 poor metabolizers, no dosage adjustment is needed. Similar to adults, pediatric patients who have the poor metabolizer genotype of CYP2C19 (CYP2C19 *2/*2) exhibited greater than a 6-fold increase in AUC compared to pediatric extensive (CYP2C19 *1/*1) and intermediate (CYP2C19 *1/*x) metabolizers. Poor metabolizers exhibited approximately 10-fold lower apparent oral clearance compared to extensive metabolizers. Pharmacokinetics: Pantoprazole metabolism is independent of the route of administration (intravenous or oral).	AUC versus NM+IM: PM: 600%

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

Risk group	UM with inducers of CYP2C19 and/or CYP3A4

Comments:

- Only kinetic studies were included with data on AUC, steady state concentration or clearance in comparison with NMs and with data on PM or on patients with the *17-variant.
  Studies with eradication therapy based on two or four medicines were not included in the status report, nor studies in which the dose of the PPI was lower than the dose registered for eradication in the Netherlands.
- 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. Comment KNMP Medicine Information Centre: 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. The latter is confirmed in the SmPC Pantoprazole 04-09-09. Sakurai et al., 2007 found no increase in the plasma concentration of lansoprazole from Day 1 to Day 5 following intravenous administration.
- **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'. However, CPIC dosing recommendations for PPIs do not differ between *1/*17 and *1/*1, between IM and 'likely IM' and between PM and 'likely PM'. The summary below uses the KNMP definitions for NM, PM, IM and UM.
    CPIC indicates that there is a substantial body of evidence linking CYP2C19 genotype with variability in plasma concentrations and efficacy of first-generation PPIs, like pantoprazole. CPIC states that the evidence associating CYP2C19 genotype with pantoprazole plasma concentrations was graded as high (i.e. evidence includes consistent results from well-designed, well-conducted studies). CPIC indicates that multiple studies have shown that the

CYP2C19 IM and PM phenotypes are associated with decreased clearance and increased plasma concentrations of first generation PPIs leading to increased treatment success compared with CYP2C19 NM, including for H. pylori infection and erosive esophagitis (Furuta T et al. Effect of genetic differences in omeprazole metabolism on cure rates for Helicobacter pylori infection and peptic ulcer. Ann Intern Med 1998;129:1027-30, Ichikawa H et al. Rapid metabolizer genotype of CYP2C19 is a risk factor of being refractory to proton pump inhibitor therapy for reflux esophagitis. J Gastroenterol Hepatol 2016;31:716-26, and Lin YA et al. Effect of CYP2C19 gene polymorphisms on proton pump inhibitor, amoxicillin, and levofloxacin triple therapy for eradication of Helicobacter Pylori. Med Sci Monit 2017;23:2701-7). CPIC states that, in contrast, CYP2C19 *1/*17 and UM have increased PPI clearance and decreased plasma concentrations compared with CYP2C19 *1/*1, which may increase risk of treatment failure compared with CYP2C19 *1/*1, IM, and PM (Sim SC et al. A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. Clin Pharmacol Ther 2006;79:103-13 and Gawrońska-Szklarz 2012). CPIC indicates that it is important to note that most CYP2C19 studies evaluating PPIs were conducted in Asian populations, in whom the frequency of the increased function CYP2C19*17 allele is low compared with non-Asians; therefore, few studies including CYP-2C19 *1/*17 and UM have been published to date. CPIC indicates that prescribing recommendations for CYP2C19 *1/*17 and UM in the CPIC guideline were based on pharmacokinetic differences versus *1/*1 and differences in PPI effectiveness between *1/*1 and IM/PM.

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

CPIC indicates that, following administration of standard doses of first-generation PPIs, CYP2C19 IM and PM experience higher PPI AUC (3-14-fold) and maximum plasma drug concentration (2-6-fold) compared with CYP-2C19 *1/*1 as a result of reduced PPI clearance via the CYP2C19 pathway (Chang M et al. Interphenotype differences in disposition and effect on gastrin levels of omeprazole–suitability of omeprazole as a probe for CYP2C19. Br J Clin Pharmacol 1995;39:511-8, Tanaka M et al. Stereoselective pharmacokinetics of pantoprazole, a proton pump inhibitor, in extensive and poor metabolizers of S-mephenytoin. Clin Pharmacol Ther 2001;69:108-13, Kim K-A et al. Enantioselective disposition of lansoprazole in extensive and poor metabolizers of CYP2C19. Clin Pharmacol Ther 2002;72:90-9, and He N et al. Inhibitory effect of troleandomycin on the metabolism of omeprazole is CYP2C19 genotype-dependent. Xenobiotica 2003;33:211-21). CPIC indicates that the increased PPI exposure in CYP2C19 IM and PM has been linked to improved acid suppression (i.e., higher intragastric pH and longer time with pH > 4.0) and improved therapeutic benefits. CPIC states, that. thus, CYP2C19 IM and PM are considered to be “therapeutically advantaged” compared with *1/*1 in terms of efficacy (Furuta T et al. CYP2C19 genotype status and effect of omeprazole on intragastric pH in humans. Clin Pharmacol Ther 1999;65:552-61, Shimatani T et al. Effect of omeprazole 10 mg on intragastric pH in three different CYP2C19 genotypes, compared with omeprazole 20 mg and lafutidine 20 mg, a new H2-receptor antagonist. Aliment Pharmacol Ther 2003;18:1149-57, Park S et al. Effects of CYP2C19 genetic polymorphisms on PK/PD responses of omeprazole in Korean healthy volunteers. J Korean Med Sci 2017;32:729-36, Chen 2010, and Kurzawski 2006). CPIC indicates that, however, it has been suggested that continued inhibition of acid secretion in individuals taking PPIs chronically who are genotyped as CYP2C19 IM or PM may have a higher risk of PPI-related adverse events compared with NM or UM phenotypes (El Rouby N et al. Proton pump inhibitors: from CYP2C19 pharmacogenetics to precision medicine. Expert Opin Drug Metab Toxicol 2018;14:447-60). CPIC states that, while the current data are insufficient to make strong dosing recommendations, potential associations of CYP2C19 phenotype and incidence of adverse events (e.g., infections) are emerging (Bernal CJ et al. CYP2C19 phenotype and risk of proton pump inhibitor-associated infections. Pediatrics 2019;144:e20190857). CPIC indicates, that, therefore, for CYP2C19 IM and PM, it is recommended to initiate standard daily dosing to maximize the likelihood of efficacy and, once efficacy is achieved, consider a 50% reduction in the daily dose in the setting of chronic PPI therapy (beyond 12 weeks) to minimize the risk of adverse events from prolonged acid suppression. CPIC indicates, that if a dose reduction is made, monitoring for continued efficacy is recommended. In addition, CPIC indicates that additional studies that investigate the relationship between CYP2C19 genotype and incidence of PPI-related adverse events are needed.

CPIC indicates that the phenotypes of *1/*17 and UM are driven by the presence of the increased function CYP-2C19*17 allele. CPIC states, that due to the relatively recent discovery of this variant (Sim SC et al. A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. Clin Pharmacol Ther 2006;79:103-13) and because the majority of studies describing associations between CYP2C19 genotype, pharmacokinetics, and pharmacodynamics of PPIs were conducted in Asian populations in whom the CYP2C19*17 allele occurs less frequently, there are limited data on the relationship between CYP2C19*17, pharmacokinetic parameters, acid secretion indices, and therapeutic outcomes in CYP2C19 *1/*17 and UM. CPIC states that additional studies with CYP2C19 *1/*17 and UM are needed. CPIC indicates that, nevertheless, the low PPI exposure documented in patients who are CYP2C19 UM compared with

*1/*1, IM, and PM suggests that these individuals may benefit from higher-than-standard daily doses of PPIs. CPIC indicates, that, therefore, it is recommended to increase the starting daily dose by 100% in CYP2C19 UM. For *1/*17, CPIC gives the same therapeutic recommendation as for *1/*1.
CPIC indicates that the plasma half-life of PPIs is short (~ 30 minutes to 5 hours), but the biological effects they exert are much longer, as it takes ~ 54 hours to regenerate new acid pumps after inactivation by PPIs. CPIC indicates, that studies have documented that daily doses administered two to four times daily may result in improved efficacy compared with the same total daily dose given once daily (Furuta T et al. Pharmacogenomics-based tailored versus standard therapeutic regimen for eradication of H. pylori. Clin Pharmacol Ther 2007;81:521-8 and Ormeci A et al. Can Helicobacter pylori be eradicated with high-dose proton pump inhibitor in extensive metabolizers with the CYP2C19 genotypic polymorphism? Eur Rev Med Pharmacol Sci 2016;20:1795-7). CPIC indicates that, although adherence to PPI dosing three to four times per day to overcome the short half-life may be challenging, it is recommended that increased PPI doses (50–100%) be administered as twice daily dosing, and more frequent dosing intervals could be considered for increased benefit, with the caveat that this dosing regimen may compromise compliance.

Dosing recommendations for pantoprazole based on CYP2C19 phenotype		
Phenotype	Therapeutic recommendation	Classification of recommendation
UM	Increase starting daily dose by 100%. Daily dose may be given in divided doses. Monitor for efficacy.	Optional[a]
NM	Initiate standard starting daily dose. Consider increasing dose by 50–100% for the treatment of H. pylori infection and erosive esophagitis. Daily dose may be given in divided doses. Monitor for efficacy.	Moderate[b]
IM	Initiate standard starting daily dose. For chronic therapy (> 12 weeks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy	Optional[a]
PM	Initiate standard starting daily dose. For chronic therapy (> 12 weeks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy	Moderate[b]

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

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

With regard to paediatrics, CPIC indicates that In children older than one year of age, there is emerging evidence that CYP2C19 genetic variation influences PPI pharmacokinetics and response (Bernal CJ et al. CYP2C19 phenotype and risk of proton pump inhibitor-associated infections. Pediatrics 2019;144:e20190857, Knebel W et al. Population pharmacokinetic modeling of pantoprazole in pediatric patients from birth to 16 years. J Clin Pharmacol 2011;51:333-45, Shakhnovich V et al. A population-based pharmacokinetic model approach to pantoprazole dosing for obese children and adolescents. Paediatr Drugs 2018;20:483-95, and Kearns 2008). CPIC indicates that CYP2C19 *1/*17 and UM have been associated with decreased efficacy compared with PM and *1/*1 when treating paediatric GERD and eosinophilic esophagitis (Franciosi JP et al. Association between CYP2C19*17 alleles and pH probe testing outcomes in children with symptomatic gastroesophageal reflux. J Clin Pharmacol 2018;58:89-96, Franciosi JP et al. Association between CYP2C19 extensive metabolizer phenotype and childhood anti-reflux surgery following failed proton pump inhibitor medication treatment. Eur J Pediatr 2018;177:69-77, and Mougey EB et al. CYP2C19 and STAT6 variants influence the outcome of proton pump inhibitor therapy in pediatric eosinophilic esophagitis. J Pediatr Gastroenterol Nutr 2019;69:581-7). CPIC indicates that the CYP2C19 PM phenotype is associated with higher rates of respiratory and gastrointestinal infections than *1/*1, *1/*17, or UM (Lima JJ et al. Association of CYP2C19 polymorphisms and lansoprazole-associated respiratory adverse effects in children. J Pediatr 2013;163:686-91). In addition, CPIC indicates that a recent pilot study of CYP2C19-genotype-guided dosing of PPIs in children has been promising, and additional studies are ongoing (Cicali EJ et al. Novel implementation of genotype-guided proton pump inhibitor medication therapy in children: a pilot, randomized, multisite pragmatic trial. Clin Transl Sci 2019;12:172-9 and Tang M et al. Genotype tailored treatment of mild symptomatic acid reflux in children with uncontrolled asthma (GenARA): Rationale and methods. Contemp Clin Trials 2019;78:27-33). CPIC states that these reports support genotype-based optimization of PPI therapy for children. CPIC indicates that, however, very low clearance in preterm infants and infants less than 2-3 months of age (Knebel W et al. Population pharmacokinetic modeling of pantoprazole in pediatric patients from birth to 16 years. J Clin Pharmacol 2011;51:333-45) makes recommendations in the neonatal population difficult to support.
On 31-7-2024, there was not a more recent version of the recommendations present on the CPIC-site.

Date of literature search: 18 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	4 A	Yes	Yes	

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

Mechanism:
Pantoprazole is primarily metabolised by CYP2C19 and CYP3A4/5 to inactive metabolites. A reduced CYP2C19 activity results in higher plasma concentrations and a higher pantoprazole AUC 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.

Clinical Implication Score:

Table 1: Definitions of the available Clinical Implication Scores

Potentially beneficial	PGx testing for this gene-drug pair is potentially beneficial. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guideline	0-2 +
Beneficial	PGx testing for this gene-drug pair is beneficial. It is advised to consider genotyping the patient before (or directly after) drug therapy has been initiated to guide drug and dose selection	3-5 +
Essential	PGx testing for this gene-drug pair is essential for drug safety or efficacy. Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection	6-10 +

Table 2: Criteria on which the attribution of Clinical Implication Score is based

Clinical Implication Score Criteria	**Possible Score**	**Given Score**
Clinical effect associated with gene-drug interaction (drug- or diminished efficacy-induced)		
• CTCAE Grade 3 or 4 (clinical effect score D or E)	+	
• CTCAE Grade 5 (clinical effect score F)	++	
Level of evidence supporting the associated clinical effect grade ≥ 3		
• One study with level of evidence score ≥ 3	+	
• Two studies with level of evidence score ≥ 3	++	
• Three or more studies with level of evidence score ≥ 3	+++	
Number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3		
• 100 < NNG ≤ 1000	+	
• 10 < NNG ≤ 100	++	
• NNG ≤ 10	+++	
PGx information in the Summary of Product Characteristics (SmPC)		
• At least one genotype/phenotype mentioned	+	+
OR		
• Recommendation to genotype	++	
OR		
• At least one genotype/phenotype mentioned as a contra-indication in the corresponding section	++	
Total Score:	10+	1+
Corresponding Clinical Implication Score:		Potentially beneficial