CYP2C19: lansoprazole 2502 to 2504

amoxi = amoxicillin, AUC = area under the concentration-time curve, CI = confidence interval, clari = clarithromycin, Cl_{or} = oral clearance, C_{ss} = steady state plasma concentration, eGFR = estimated glomerular filtration rate, esome = esomeprazole, GERD = gastroesophageal reflux disease, Hp = Helicobacter pylori, HR = hazard ratio, HR_{adj} = adjusted hazard ratio, 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, OR_{adj} = adjusted 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).

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:

Lansoprazole is primarily converted by CYP2C19 and CYP3A4/5 to inactive metabolites (respectively 5'-hydroxy lansoprazole and lansoprazole sulphone). 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 lansoprazole AUC, so an increase in CYP2C19 activity (ultra-rapid metaboliser (UM)) is expected to result in a lower lansoprazole AUC.

IM and PM: The result of treatment with lansoprazole for each indication was either not significantly different or improved for IM and PM patients. Increased therapeutic efficacy in IM and PM patients for the indications reflux oesophagitis (significant in 4 of the 5 studies for PM and IM (Furuta 2009, Kawamura 2007, Kawamura 2003, and Furuta 2002), and insignificant in the only study for IM+PM) and eradication of Helicobacter pylori (significant in 4 of the 6 meta-analyses and 8 of the 13 studies for PM (Morino 2021; Fu 2021; Tang 2013; Zhao 2008; Liou 2016; Furuta, Aliment Pharmacol Ther 2007; Sugimoto 2006; Furuta, Clin Pharmacol Ther 2007; Furuta, Clin Gastroenterol Hepatol 2005; Furuta 2004; Kawabata 2003; Furuta, Clin Pharmacol Ther 2001;69:158-68), 5 of the 6 meta-analyses and 7 of the 11 studies for IM (Zhao 2022; Morino 2021; Fu 2021; Tang 2013; Zhao 2008; Furuta, Aliment Pharmacol Ther 2007; Sugimoto 2006; Furuta, Clin Pharmacol Ther 2007; Furuta, Clin Gastroenterol Hepatol 2005; Furuta 2004; Kawabata 2003; Furuta, Clin Pharmacol Ther 2001), and insignificant in the only study for IM+PM), and for increasing the gastric pH (significant in 5 of the 6 studies for PM (Sugimoto 2007, Furuta, Aliment Pharmacol Ther 2005; Shirai 2002; Furuta 2001;70:484-92; Adachi 2000) and 2 of the 8 studies for IM (Hunfeld 2008 and Furuta 2001;70:484-92), suggested that the dose in NMs is actually suboptimal. There are insufficient data for peptic ulcer/bleeding.

Adverse events were only investigated in two studies. Lima 2013 did not find an increase of the percentage of paediatric patients with an adverse event and in the percentage with a sore throat for IM+PM treated for 6 months, but did find an increase in the percentage with upper respiratory infection (cold) for IM+PM. However, this increase was only reported in one article and does not concern a known adverse effect of proton pump inhibitors. There is evidence that proton pump inhibitors increase the risk of infection with Clostridium difficile and there are indications for an increase in pneumonia risk, but an increased risk in upper respiratory infections has only been reported in this single article. In addition, the postulated mechanism of a less acidic gastric environment for the enhanced Clostridium infection risk will not apply to upper respiratory infections. Finally, it concerns a subjective outcome in a special patient group (children with poorly controlled asthma and asymptomatic acid reflux), so it is doubtful whether the result can be generalised to the normal patient population. Fukui 2024 found a shorter time to a 30% decrease in estimated glomerular filtration rate (eGFR) for PM compared to IM+NM in patients treated for at least 30 days. However, results were not consistent with the time to a 30% decrease in eGFR increasing in the order IM<NM<PM instead of NM<IM<PM. In addition, because significance of the difference between PM and NM was not determined, it was not clear from this study if the risk for PM was also increased compared to

NM. Moreover, the shorter time in PM was only reported in one article. Finally, it would be difficult to find a good alternative for lansoprazole in PM, because dose reduction would also lead to a decrease in therapeutic efficacy and for esomeprazole, which is not clinically significantly influenced by PM, Fukui 2024 found Kaplan-Meier curves for PM and NM+IM that closely resembled those for lansoprazole and PM instead of those for lansoprazole and IM+NM. For these reasons, the KNMP Pharmacogenetics Working Group concluded that there is not enough evidence for an increase in adverse events in PM and IM. Because of the observed kinetic effect and increase in therapeutic efficacy, the KNMP Pharmacogenetics Working Group concluded that there is a gene-drug interaction. However, due to the lack of convincing evidence for negative effects, it is not useful or necessary to modify the treatment with lansoprazole for IM and PM patients (yes/no-interactions).

UM: No studies were found for UM. However, treatment of NM patients delivered less therapeutic efficacy on reflux oesophagitis and eradication of Helicobacter pylori than it did for IM and PM patients. 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).
The calculated dose increase is based on the dose increase needed to achieve a similar exposure in NM patients as in 75 PM patients (the weighted mean was a dose increase up to 380% of the normal dose (239-856%; median 456%)). The KNMP Pharmacogenetics Working Group translated this to a figure of 400% to be achievable in practice.

You can find a detailed overview of the observed kinetic and clinical effects in the background information text of the gene-drug interactions 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 lansoprazole 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):
Lansoprazole 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 Dutch 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. 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 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 2009, references are listed based on the date of publication only. For the period before, GERD-references are listed first, followed by Hp-references, and kinetic 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	3	348 patients were treated with lansoprazole for at least 30 days. Follow-up was for 180 days after treatment initiation. Administration of lansoprazole was for a period of 31-5,681 days (median 501 and 400 days for non-PM and PM, respectively, so longer than the follow-up period). 40 patients (11.5%) had a 30% decrease in estimated glomerular filtration rate (eGFR) during the follow-up period. Non-PM patients used less often NSAIDs and more often	Authors' conclusion: 'This retrospective study showed that CYP2C19 metabolizer status was associated with the time to a 30% eGFR decrease in patients

<table>
<tr>
<td>retrospective cohort study.
Clin Pharmacol Ther 2024;115:1141-51.
PMID: 38258325.

ref. 1, continuation</td>
<td>PM: C</td>
<td>angiotensin receptor blockers as concomitant medication than PM patients (5.7% versus 15.6% and 27.2% versus 3.9%, respectively). The duration of concomitant treatment with NSAIDs was a median of 8 days (range 1-38 days) in the PM group and a median of 9 days (range 1-180 days) in the non-PM group.
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 lansoprazole. However, multivariate Cox regression analysis was performed to correct for concomitant medications and co-existing illnesses.
Multivariate Cox regression analysis adjusted for sex (male), age (aged 65 or more years), initial dose of lansoprazole (15 mg), baseline eGFR (≥ 60 mL/min/1.73 m^2), hypertension (yes), diabetes (yes), hyperuricemia (yes), myocardial infarction (yes), cerebrovascular disease (yes), malignant tumour (yes), NSAIDs (yes), vancomycin (yes), and edaravone (yes). Multivariate analysis did not adjust for angiotensin receptor blockers, ACE inhibitors and contrast medium, because angiotensin receptor blockers were shown to be collinear with hypertension and ACE inhibitors and contrast medium with a history of myocardial infarction. However, whereas there was no significant difference or trend for a difference between the presence or absence of hypertension and history of a myocardial infarction between the CYP2C19 phenotypes, there was a significant difference between the concomitant use of angiotensin receptor blockers (which was 8 and 6 times less frequent in PM than in NM and IM, respectively) and a trend for a difference between the phenotypes for ACE inhibitors (P = 0.055, with the frequency for IM being 1.8 and 2 times lower than for NM and PM, respectively) and contrast medium (P = 0.081, with the frequency for NM being 2.3 and 2.5 times lower than for IM and PM, respectively). ACE inhibitors and contrast medium showed a significant effect on the time to a 30% decrease in eGFR in univariate analysis, whereas angiotensin receptor blockers did not.

Genotyping:
- 114x NM (112x *1/*1 and 2x *1/*17)
- 183x IM
- 51x PM

Results:
<table>
<tr><td colspan="4">Time to a 30% decrease in eGFR:</td></tr>
<tr><td></td><td>comparison group</td><td></td><td>incidence of patients with a 30% decrease in eGFR in the comparison group</td></tr>
<tr><td rowspan="3">PM</td><td>*1/*1</td><td>significance not determined</td><td>13.4%</td></tr>
<tr><td rowspan="2">IM+NM</td><td>HR = 2.43 (95% CI: 1.21-4.87) (S)</td><td rowspan="2">9.8%</td></tr>
<tr><td>Multivariate regression analysis showed the PM phenotype to</td></tr>
</table>
</td>
<td>treated with lansoprazole, but not with esomeprazole, rabeprazole, or vonoprazan.’</td>
</tr>
</table>

<table>
<tr>
<td>ref. 1, continuation</td>
<td>IM: AA</td>
<td>
<table>
<tr><td></td><td></td><td>be an independent predictor of time to a 30% decrease in eGFR: HR_{adj} = 2.14 (95% CI: 1.06-4.30) (S).
Note: the other two independent predictors identified (hypertension and a history of myocardial infarction) were much stronger with HR_{adj} of 4.01 and 3.80 respectively.</td><td></td></tr>
<tr><td></td><td>IM</td><td>HR = 3.03 (95% CI: 1.37-6.67) (S)</td><td>7.9%</td></tr>
<tr><td>IM</td><td>*1/*1</td><td>NS</td><td>13.4%</td></tr>
</table>
NOTES:
- The numerical results did not show a consistent effect of genetically reduced CYP2C19 on (the time to) a 30% decrease in eGFR. Whereas the time to a 30% decrease in eGFR was higher for PM compared to *1/*1 over the whole follow-up period, it was lower for IM compared to *1/*1 over this period. In addition, the ratio of the incidence of patients with a 30% decrease in eGFR in the 180-days follow-up period was 1:0.6:1.6 for *1/*1:IM:PM.
As a result, the significance for PM compared to NM seems to be driven by the low values observed for IM, as also shown by both the HR for PM compared to IM being larger instead of smaller than that for PM compared to IM+IM and it having a P value that is a factor 2 smaller (0.006 for PM compared to IM and 0.012 for PM compared to IM+NM).
- The inverse Kaplan-Meier curve for 145 IM+PM treated with esomeprazole showed more similarity with the PM curve than with the IM+NM curve for lansoprazole, suggesting that the risk for PM on lansoprazole is not unusually high.

NOTE: The patient population in this study was enriched for patients with a history of myocardial infarction (a strong risk factor for a 30% decrease in eGFR), because in the authors hospital, CYP2C19 genotyping is routinely performed for patients prescribed thienopyridines for selection of clopidogrel or prasugrel. This indicates that the incidence of a 30% decrease in eGFR in this study is probably considerably higher than that in the full population of lansoprazole users.

NOTE: Genotyping was for *2, *3, and *17. These are the most important gene variants in this Japanese population.
</td>
<td></td>
</tr>
<tr>
<td>ref. 2, 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.</td>
<td>3</td>
<td>Meta-analysis of 11 observational, randomised controlled or comparative studies with a total of 927 patients (389 NM, 401 IM, and 137 PM) with H. pylori infection treated with triple or quadruple therapy with lansoprazole. 10 of the included studies used triple therapy and 1 study with 98 patients (40 NM, 47 IM, and 11 PM) used quadruple therapy. Lansoprazole doses in the trials were not mentioned.
Six of the studies in this meta-analysis were also included in this risk analysis separately (Inaba 2002; Kawabata 2003; Miki 2003; Furuta, Clin Gastroenterol Hepatol 2005; Sugimoto 2007; Lee 2010).
Five of the studies in this meta-analysis were also included in the meta-analyses of Fu 2021 and Morino 2021, four in</td>
<td>Authors' conclusion: 'Carriers of CYP-2C19 loss-of-function variant alleles (IM and PM) exhibit a significantly greater cure rate of H. pylori than noncarriers (NM) regardless of other factors. ..... There was a significantly lower H. pylori cure rate in</td>
</tr>
</table>

<table>
<tr>
<td>PMID: 36278195.

ref. 2, continuation</td>
<td>PM: AA

IM: AA#</td>
<td>the meta-analysis of Tang 2013, and three in the meta-analyses of Zhao 2008 and Padol 2006.
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 lansoprazole studies.

Results:
<table>
<tr><td colspan="2">H. pylori eradication rate compared to NM (eradication in 76.1% of patients):</td></tr>
<tr><td rowspan="3">PM</td><td>NS</td></tr>
<tr><td>The H. pylori eradication rate for PM was 83.9%.</td></tr>
<tr><td>Note: the smallest OR for PM (OR = 0.26, indicating a worse eradication rate in PM) was found in the study investigating quadruple therapy. This value was halve the lowest value in a triple therapy study.
7 of the 11 included studies found a better eradication rate in PM.</td></tr>
<tr><td rowspan="2">IM</td><td>OR = 1.85 (95% CI: 1.25-2.78) (S)</td></tr>
<tr><td>The H. pylori eradication rate for IM was 85.6%.</td></tr>
<tr><td colspan="2">For both comparisons, there was no heterogeneity between the studies.</td></tr>
</table>
</td>
<td>NM subjects than that in IM subjects when treated with omeprazole and lansoprazole, but not rabeprazole, esomeprazole, or pantoprazole.’</td>
</tr>
<tr>
<td>ref. 3, 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 9 randomised controlled trials with a total of 798 patients (299 NM, 373 IM, and 126 PM) with H. pylori infection treated with lansoprazole/amoxicillin/clarithromycin triple therapy. The lansoprazole dose used was 30 mg twice a day during one week (eight studies) or 60 mg twice a day during one or two weeks (one study).
Five of the studies in this meta-analysis were also included in this risk analysis separately (Inaba 2002, Kawabata 2003, Miki 2003, Furuta, Clin Pharmacol Ther 2007, and Lee 2010).
Seven of the studies in this meta-analysis were also included in the meta-analysis of Tang 2013, six in the meta-analysis of Fu 2021, five in the meta-analysis of Padol 2006, and four in the meta-analysis of 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.
Quality of the included studies was not assessed.
Possible publication bias was analysed by funnel plot only and only for all studies (all PPIs), not for the subgroup of lansoprazole studies.

Results:
<table>
<tr><td>H. pylori eradication rate compared to NM (eradication in 73.6% of patients):</td></tr>
</table>
</td>
<td>Authors’ conclusion: ‘The cure rate of omeprazole and lansoprazole-containing eradication regimens differed among CYP2C19 genotypes.’</td>
</tr>
</table>

<table>
<tr><td>ref. 3, continuation</td><td>IM: AA#

PM: AA#</td><td><table>
<tr><td>IM</td><td>RR = 1.44 (95% CI: 1.09-1.99) (S)</td></tr>
<tr><td></td><td>The H. pylori eradication rate for IM was 80.7%.</td></tr>
<tr><td>PM</td><td>RR = 2.47 (95% CI: 1.44-4.23) (S)</td></tr>
<tr><td></td><td>The H. pylori eradication rate for PM was 89.7%.</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
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

IM: AA#

PM: AA#</td><td>Meta-analysis of 13 Asian studies (10 randomised controlled trials and 3 cohort studies) with a total of 2135 patients (771 NM, 1028 IM, and 336 PM) with H. pylori infection treated with triple therapy. The lansoprazole dose used was 30 mg twice a day in 12 studies (during 1 week in 11 studies and during 2 weeks in 1 study) and 30 mg once a day during 1 week in 1 study including 47 patients (5 NM, 28 IM, and 14 PM). 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). One of the ten included randomised trials had a low risk of bias in 5 domains and an uncertain risk in 2 domains (allocation concealment and selective reporting), six had a low risk of bias in 4 domains and an uncertain risk in 3 domains (allocation concealment, selective reporting, and other in four studies and allocation concealment, blinding of participants and personnel, and other in two studies), two had a low risk of bias in 4 domains, an uncertain risk in 2 domains (allocation concealment and selective reporting in one study and allocation concealment and other in the other study) and a high risk of bias in one domain (other and incomplete outcome data, respectively), and the tenth had a low risk of bias in 3 domains, an uncertain risk in 3 domains (allocation concealment, selective reporting, and other) and a high risk of attrition bias due to incomplete outcome data. One of the three included cohort studies scored 7 points on the Newcastle-Ottawa Scale, one 6 points and the third 5 points.
Nine of the studies in this meta-analysis were also included in this risk analysis separately (Furuta, Clin Pharmacol Ther 2001;69:158-68; Inaba 2002; Kawabata 2003; Miki 2003; Furuta 2004; Furuta, Clin Gastroenterol Hepatol 2005; Sugimoto 2006; Furuta, Clin Pharmacol Ther 2007; Lee 2010).
Eight of the studies in this meta-analysis were also included in the meta-analysis of Zhao 2008, six in the meta-analysis of Tang 2013, and four in the meta-analysis of Padol 2006.
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 lansoprazole 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 71.1% of patients):</td></tr>
<tr><td>IM</td><td>OR = 2.64 (95% CI: 1.71-4.08) (S)</td></tr>
<tr><td></td><td>The H. pylori eradication rate for IM was 86.2%.</td></tr>
<tr><td>PM</td><td>OR = 4.23 (95% CI: 2.36-7.57) (S)</td></tr>
</table></td><td>Authors' conclusion: 'Our results also indicated that the efficacies of omeprazole and lansoprazole for treating patients with H. pylori infection were affected by the status of the CYP2C19 genotype.'</td></tr>
</table>

ref. 4, continuation		The H. pylori eradication rate for PM was 92.2%. NOTE: The study using a lower lansoprazole dose (30 mg once a day) than that used in the Netherlands, showed the highest influence of PM and IM (OR 2.6 and 3.6 times the highest OR found in the other 12 included studies, respectively). This indicates that the ORs found in the meta-analysis would be somewhat smaller if this study would not have been included. Heterogeneity between the studies was significant and substantial for the comparison of IM and NM and did not reach significance for the comparison of PM and NM (P = 0.126).	
ref. 5, Hp Liou JM et al. Sequential therapy for 10 days versus triple therapy for 14 days in the eradication of Helicobacter pylori in the community and hospital populations: a randomised trial. Gut 2016;65:1784-1792. PubMed PMID: 26338825.	3 PM: AA#	335 hospital patients and 223 community patients with H. pylori infection were treated with triple therapy with lansoprazole 30 mg twice daily for 14 days. H. pylori eradication was defined as a negative ^{13}C-urea breath test at least 6 weeks after completion of therapy. Use of other antibiotics within 4 weeks was excluded, but other relevant co-medication was not. Adjusted ORs were determined with multiple logistic regression analysis. Genotyping: - 481x (NM + IM) - 77x PM Results: H. pylori eradication rate compared to NM+IM (eradication in 84.8% of patients): PM: x 1.1 (OR_{adj} = 0.2; 95% CI: 0.0-1.0; p = 0.046) (S)	Authors' conclusion: 'The efficacy of triple therapy for 14 days, but not sequential therapy for 10 days, was affected by CYP2C19 polymorphism.'
ref. 6, Hp Liou JM et al. Levofloxacin sequential therapy vs levofloxacin triple therapy in the second-line treatment of Helicobacter pylori: a randomized trial. Am J Gastroenterol 2016;111:381-7. PubMed PMID: 26832653.	3 PM: AA	256 hospital or community patients with H. pylori infection who failed clarithromycin-based eradication therapy, were treated with levofloxacin-based triple therapy with lansoprazole 30 mg twice daily for 10 days. H. pylori eradication was defined as a negative ^{13}C-urea breath test at least 6 weeks after completion of therapy. Relevant co-medication was not excluded. Genotyping: - 226x (NM + IM) - 30x PM Results: H. pylori eradication rate compared to NM+IM (eradication in 78.3% of patients): PM: NS Note: Genotyping was for *2 and *3. These are the most important gene variants in this Taiwanese population.	Authors' conclusion: 'The efficacies of levofloxacin sequential therapy and levofloxacin triple therapy were not affected by the CYP2C19 polymorphism.'
ref. 7, GERD Lang JE et al. Lansoprazole is associated with worsening asthma control in children with the CYP2C19 poor metabolizer phenotype. Ann Am Thorac Soc 2015 Jun;12:878-85. PubMed PMID: 25844821.	3	Data were analysed for the same patient group as in Lima 2013. The total number of patients (n = 138) and the number of NM+UM and IM+PM for which data were available differed slightly. The Asthma Control Questionnaire measures five patient-reported asthma symptoms, the need for bronchodilators and pulmonary function on a seven-point scale (higher score indicating worse asthma). A 0.4- to 0.5-point change in this score reflects a clinically important difference in asthma control. The asthma control test (ACT) is a 5-item scale and the childhood ACT a 7-item scale for children younger than 12 years of age (n = 71), both with a higher score indicating better asthma control. The minimal important difference is 2-3 for the ACT and 2 for the childhood ACT. The Asthma	Authors' conclusion: 'Children with the PM phenotype developed worse asthma control after 6 months of lansoprazole treatment for poorly controlled asthma. Increased exposure to proton pump inhibitor may worsen asthma control by altering responses to respirato-

<table>
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<td>ref. 7, continuation</td>
<td>IM+PM: A</td>
<td>
Symptom Utility Index measures asthma symptoms and medication side-effects, with a higher score reflecting reduced asthma symptoms. The minimal important difference of this scale is 0.09 (the score ranges from 0 to 1).
The Paediatric Gastroesophageal Reflux Disease Symptom Assessment Score measures 10 items on an 8-point scale with higher score indicating greater severity.
Self-reported upper respiratory infections were assessed by monthly interviews.

Genotyping:
- 94x (NM + UM)
- 44x (IM + PM)

Results:
<table>
<tr><td colspan="4">IM+PM versus NM+UM:</td></tr>
<tr><td></td><td></td><td></td><td>value for NM+UM</td></tr>
<tr><td rowspan="3">change in asthma control questionnaire (ACQ)</td><td>after 3 months</td><td>NS</td><td>- 0.12</td></tr>
<tr><td>after 6 months</td><td>x -1.2 (S)</td><td>- 0.13</td></tr>
<tr><td colspan="2">The change for IM+PM was also worse than the change for placebo-treated patients (S). However, the difference with NM+UM after 6 months was < 0.4 and thus clinically not important.</td></tr>
<tr><td rowspan="3">difference in ACQ between those with and without a recent upper respiratory infection</td><td>all monthly assessments</td><td>NS</td><td>0.34</td></tr>
<tr><td>after 6 months</td><td>NS</td><td>0.28</td></tr>
<tr><td colspan="2">On average the ACQ was 0.3 points higher in participants with a recent upper respiratory infection (S, but not clinically important)</td></tr>
<tr><td rowspan="3">change in childhood asthma control test (< 12 years of age)</td><td>after 3 months</td><td>NS</td><td>1.1</td></tr>
<tr><td>after 6 months</td><td>x 0 (NS, trend, p = 0.07)</td><td>2.0</td></tr>
<tr><td colspan="2">The change for IM+PM was also numerically worse than the change for placebo-treated patients (NS, trend, p = 0.08). However, the difference with NM+UM after 6 months was 2.0 and thus marginally clinical important.</td></tr>
<tr><td rowspan="3">change in asthma control test (≥ 12 years of age)</td><td>after 3 months</td><td>NS</td><td>0.7</td></tr>
<tr><td>after 6 months</td><td>x 0.13 (NS, trend, p = 0.10)</td><td>1.5</td></tr>
<tr><td colspan="2">The change for IM+PM was also numerically worse than the change for placebo-treated patients (NS, trend, p = 0.09). However, the difference with NM+UM after 6 months was < 2 and thus clinically not important.</td></tr>
<tr><td rowspan="2">change in Asthma Symptom</td><td>after 3 months</td><td>NS</td><td>0.02</td></tr>
<tr><td>after 6 months</td><td>NS</td><td>0.04</td></tr>
</table>
</td>
<td>ry infections.’</td>
</tr>
</table>

<table>
<tr>
<td>ref. 7, continuation</td>
<td></td>
<td>
<table>
<tr><td>Utility Index</td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">change in GERD Symptom Assessment Score</td><td>after 3 months</td><td>NS</td><td>- 7</td></tr>
<tr><td>after 6 months</td><td>NS</td><td>- 6</td></tr>
<tr><td rowspan="2">change in number of daily GERD symptoms</td><td>after 3 months</td><td>NS</td><td>- 1</td></tr>
<tr><td>after 6 months</td><td>NS</td><td>- 1</td></tr>
</table>

The authors indicate that the risk-benefit relationship of proton pump inhibitor use among patients with asthma with problematic acid reflux is likely to be different than that in this cohort with asymptomatic acid reflux.
</td>
<td></td>
</tr>
<tr>
<td>ref. 8, kin
Li CY et al.
A correlative study of polymorphisms of CYP2C19 and MDR1 C3435T with the pharmacokinetic profiles of lansoprazole and its main metabolites following single oral administration in healthy adult Chinese subjects.
Eur J Drug Metab Pharmacokinet 2014;39:121-8.
PubMed PMID: 24022708.</td>
<td>3

IM: A
PM: A</td>
<td>24 healthy volunteers received a single dose of lansoprazole 30 mg.
Co-medication, alcohol and tobacco were excluded.

Genotyping:
- 10x NM
- 11x IM
- 3x PM

Results:
<table>
<tr><td colspan="2">AUC compared to NM (1.96 µg.h/ml):</td></tr>
<tr><td>IM</td><td>x 1.64 (S)</td></tr>
<tr><td>PM</td><td>x 3.16 (S)</td></tr>
</table>

Note: Genotyping was for *2 and *3. These are the most important gene variants in this Chinese population.
</td>
<td>Authors’ conclusion: ‘Compared to the CYP2C19 NMs, the CYP2C19 PM group showed slower elimination and better oral bioavailability of lansoprazole with statistically significance.’

AUC versus NM:
IM: 164%
PM: 316%</td>
</tr>
<tr>
<td>ref. 9, GERD
Lima JJ et al.
Association of CYP2C19 polymorphisms and lansoprazole-associated respiratory adverse effects in children.
J Pediatr 2013;163:686-91.
PubMed PMID: 23623526.</td>
<td>3

IM+PM: C</td>
<td>136 children of 6-17 years old with poorly controlled asthma and asymptomatic acid reflux were treated with lansoprazole for 6 months. The dose was 15 mg/day for children < 30 kg and 30 mg/day for children ≥ 30 kg.
By means of a monthly questionnaire, the presence of the following adverse events was assessed: upper respiratory infection (cold), sore throat, strep throat, bronchitis, pneumonia, ear infection, and acute sinusitis.
Plasma concentrations 2-3 hours after dosing (maximum plasma concentrations) were determined in 56 patients on lansoprazole 30 mg/day.
Relevant co-medication was not excluded.
ORs were calculated by logistic regression.

Genotyping:
- 91x (NM + UM)
- 45x (IM + PM)

Results:
<table>
<tr><td colspan="3">Adverse events for IM+PM versus NM+UM:</td></tr>
<tr><td></td><td></td><td>value for NM+UM</td></tr>
<tr><td>% of patients with upper respiratory infection (cold)</td><td>x 1.14 (S: OR versus the placebo group is significant for IM+PM (OR = 2.46), but not for NM+UM)</td><td>60%</td></tr>
<tr><td rowspan="2">% of patients with a sore throat</td><td>NS</td><td rowspan="2">45%</td></tr>
<tr><td>OR versus the placebo group is significant for both IM+PM (OR = 2.94) and</td></tr>
</table>
</td>
<td>Authors’ conclusion: ‘Lansoprazole-associated upper respiratory infections and sore throat in children are related in part to CYP2C19 haplotype. Our data suggest that lansoprazole-associated adverse events in children may be mitigated by adjusting the conventional dose in PMs. Additional studies are required to replicate our findings.’</td>
</tr>
</table>

<table>
<tr>
<td>ref. 9, continuation</td>
<td></td>
<td>
<table>
<tr><td></td><td>NM+UM (OR = 1.97)</td><td></td></tr>
<tr><td>% of patients with an adverse event</td><td>Trend for a significant OR versus placebo for IM+PM (p = 0.052), but not for NM+UM (NS)</td><td></td></tr>
<tr><td>plasma con-centration 2-3 hours after dosing</td><td>x 1.57 (S)</td><td>132 ng/ml</td></tr>
<tr><td colspan="3">For the total group, lansoprazole significantly increased the risk for upper respiratory infection, sore throat and bronchitis compared to placebo.</td></tr>
</table>

Note: Genotyping was for *2, *3, *8, *9 and *17. These are the most important gene variants in this population from the USA. The authors do not state how they classify *1/*17 and *17/*17. Most probably, they consider *17 as a wild-type allele and classify both genotypes as NM.
</td>
<td></td>
</tr>
<tr>
<td>ref. 10, 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 arms of 7 randomised controlled trials with in total 953 patients with H. pylori infection treated with triple therapy with lansoprazole. One of the trials compared lansoprazole- with lafutidine-based triple therapy. One of the trials compared lansoprazole-based triple therapy with the same therapy with additional famotidine. In one of the trials, one arm received CYP2C19- and clarithromycin resistance-guided therapy (lansoprazole 30 mg 3 or 4 times daily for NM, lansoprazole 15 mg 3 or 4 times daily for IM, and lansoprazole 15 mg 2 times daily for PM; different regimes for amoxicillin and clarithromycin). The other trials/arms used 30 mg twice daily. Risk of bias was high in 3 of the included studies, unclear in 2 studies, and low in 2 studies according to the Cochrane risk of bias tool by the following dominions: randomization method, allocation concealment, blinding, incomplete outcome data addressed and selective reporting. Five of the trials in the meta-analysis were also included in this risk analysis separately (Inaba 2002; Kawabata 2003; Miki 2003; Furuta, Clin Pharmacol Ther 2007; Lee 2010). Four of the trials in this meta-analysis were also included in the meta-analysis of Zhao 2008 and five in the meta-analysis of Padol 2006.
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 lansoprazole.

Genotyping:
- 346x NM
- 460x IM
- 147x PM

Results:
<table>
<tr><td colspan="2">H. pylori eradication rate compared to NM (eradication in 75% of patients):</td></tr>
<tr><td>PM</td><td>OR = 2.27 (95% CI: 1.30-3.97) (S)</td></tr>
<tr><td>IM</td><td>OR = 1.45 (95% CI: 1.01-2.06) (S)</td></tr>
<tr><td colspan="2">There was no significant heterogeneity between the</td></tr>
</table>
</td>
<td>Authors' conclusion: 'Carriage of CYP-2C19 loss-of-function variants is associated with increased H. pylori eradication rate in patients taking PPI-based triple therapies when omeprazole or lansoprazole is chosen.'</td>
</tr>
</table>

<table>
<tr><td>ref. 10, continuation</td><td></td><td>studies.

The authors indicate that the higher cure rate in PM compared to NM, suggests that NMs may need to take a higher-than-standard dose of lansoprazole.</td><td></td></tr>
<tr><td>ref. 11, kin
Zhang D et al.
Effects of CYP2C19 polymorphism on the pharmacokinetics of lansoprazole and its main metabolites in healthy Chinese subjects.
Xenobiotica 2011;41:511-7.
PubMed PMID: 21521077.</td><td>3

IM: AA
PM: A</td><td>24 healthy volunteers received a single dose of lansoprazole 30 mg.
Co-medication, alcohol and tobacco were excluded.

Genotyping:
- 12x NM
- 8x IM
- 4x PM

Results:<table><tr><td colspan="2">AUC compared to NM (1.60 µg.h/ml):</td></tr><tr><td>IM</td><td>x 1.62 (NS)</td></tr><tr><td>PM</td><td>x 4.56 (S)</td></tr></table>
Note: Genotyping was for *2 and *3. These are the most important gene variants in this Chinese population.</td><td>Authors’ conclusion: ‘CYP2C19 polymorphism had significant effects on the pharmacokinetics of lansoprazole and its main metabolites.’

AUC versus NM:
IM: 162%
PM: 456%</td></tr>
<tr><td>ref. 12, Hp
Tamura T et al.
Improvements in Helicobacter pylori eradication rates through clinical CYP2C19 genotyping.
Nagoya J Med Sci 2011;73:25-31.
PubMed PMID: 21614934.</td><td>3</td><td>For patients receiving eradication therapy for the first time, CYP2C19 genotype-guided eradication therapy was compared with therapy in the years before genotyping. Not-genotype-guided therapy (n = 90) consisted of therapy with lansoprazole 30 mg twice daily, amoxicillin and clarithromycin. Genotype-guided therapy (n = 124) consisted of rabeprazole or lansoprazole with amoxicillin and metronidazole for NM, whereas IM, PM, and patients refusing genotyping (n = 2) received therapy with lansoprazole, amoxicillin and clarithromycin, unless they had a history of allergy against or adverse events on any of these drugs.
Only patients treated and evaluated were included in the calculation of the eradication rate (per protocol analysis).
Cessation of smoking during the treatment period was advised.
In addition, the prevalence of NM was compared between 50 patients who failed eradication therapy in other clinics and 192 patients genotyped for inclusion in the genotype-guided group (control group). Since triple therapy with lansoprazole, amoxicillin and clarithromycin is the first-line treatment in Japan, most of the failed eradication therapies should have been lansoprazole-based.
Relevant co-medication was not excluded in either of the studies.

Genotyping genotype-guided group:
- 49x NM
- 73x (IM+PM)
- 2x unknown

Results:<table><tr><td colspan="3">H. pylori eradication rate for genotype-guided versus not-genotype guided therapy:</td></tr><tr><td></td><td></td><td>Value for not-genotype-guided therapy</td></tr><tr><td>all patients</td><td>trend for an increase (NS, p = 0.078)</td><td>80%</td></tr><tr><td>patients less than 70 years of age and not</td><td>trend for an increase (NS, p = 0.051,</td><td></td></tr></table></td><td>Authors’ conclusion: ‘This study documented an improvement in the overall eradication rate through the introduction of a routine genetic test for CYP2C19, although the effects were marginally significant only among those less than 70 years of age.’</td></tr>
</table>

ref. 12, continuation	IM+PM: AA	refusing genotyping | adjusted for age and sex) The study was underpowered. In order to have 80% power to detect a difference between eradication rates of 80% and 90%, 219 patients per arm would have been required. % of NMs compared to a population control group (34.4%): patients who failed mainly lansoprazole-based eradication therapy earlier | trend for an increase (NS, p = 0.076) Note: Genotyping was for *2 and *3. These are the most important gene variants in this Japanese population.	
ref. 13, kin Xu HR et al. The effect of CYP2C19 activity on pharmacokinetics of lansoprazole and its active metabolites in healthy subjects. Pharm Biol 2010;48:947-52. PubMed PMID: 20673183.	3 IM: A PM: A	22 healthy volunteers received a single dose of lansoprazole 30 mg. Co-medication was excluded. Genotyping: - 9x NM - 8x IM - 5x PM Results: AUC compared to NM (4.54 µg.h/ml): IM: x 2.08 (S) PM: x 8.56 (S) Note: Genotyping was for *2 and *3. These are the most important gene variants in this Chinese population.	Authors' conclusion: 'Our results indicated that there were significant differences between the NM and PM groups, and between the NM and IM groups in C_{max}, AUC_{0-t}, and AUC_{0-inf} of lansoprazole.' AUC versus NM: IM: 208% PM: 856%
ref. 14, Hp Lee JH et al. The influence of CYP2C19 polymorphism on eradication of Helicobacter pylori: a prospective randomized study of lansoprazole and rabeprazole. Gut Liver 2010;4:201-6. PubMed PMID: 20559522.	3 IM: AA PM: AA	234 patients with H. pylori infection were treated with triple therapy with lansoprazole 30 mg twice daily for 1 week. H. pylori eradication was defined as a negative ^{13}C-urea breath test 7 to 8 weeks after completion of therapy. Eradication rates were calculated by per protocol analysis. Relevant co-medication, other than PPIs, H_2 receptor antagonists, adrenocortical steroids, antibiotics or NSAIDs within the preceding month, was not excluded. Genotyping: - 85x NM - 108x IM - 41x PM Results: H. pylori eradication rate compared to NM (eradication in 74.1% of patients): IM, PM | NS for NM versus IM versus PM The authors indicate that more than 200 patients would be needed per genotype group for the numerical higher eradication rates in PM and IM to become significant. Note: Genotyping was for *2 and *3. These are the most important gene variants in this Korean population.	Authors' conclusion: 'The efficacies of triple therapies that include lansoprazole or rabeprazole are not affected by CYP2C19 genetic polymorphisms.'
ref. 15 – GERD Furuta T et al. CYP2C19 genotype is associated with symptomatic recurrence of GERD during maintenance	3	124 Hp-negative patients with GERD whose mucosal lesions had healed after lansoprazole 30 mg/day for 8 weeks. 70 patients with GERD symptoms more than once weekly, 36x NM (*1/*1), 28x IM (*1/*2 or *1/*3), 6x PM (*2/*2 or *2/*3 or *3/*3), received lansoprazole 30 mg/day maintenance therapy for 6 months. 54 patients with GERD symptoms less than once weekly,	Authors' conclusion: 'When the dose of lansoprazole is decreased, the NM genotype of CYP-2C19 appears to be a risk factor for

therapy with low-dose lansoprazole. Eur J Clin Pharmacol 2009;65:693-8. **ref. 15, continuation**	IM: AA# PM: AA#	18x NM (*1/*1), 28x IM (*1/*2 or *1/*3), 8x PM (*2/*2 or *2/*3 or *3/*3), received lansoprazole 15 mg/day maintenance therapy for 6 months or until recurrence of GERD. Co-medication was not known. NM versus IM versus PM: - OR for recurrence of GERD symptoms on lanso 15 mg/day: 1.0 : 0.40 (95% CI 0.19-0.87) : 0.19 (95% CI 0.05-0.69) - Patients on 30 mg/day maintenance dose or with recurrence of GERD symptoms on 15 mg/day (%): 96.3 : 89.3 (NS) : 71.4 (S) - The time to recurrence of GERD symptoms on 15 mg/day was less for NM (NS) Note: Genotyping was performed for *2, *3 and *17. The prevalence of *17 is very low in this (ethnically Japanese) population group.	symptomatic recurrence of GERD. The CYP2C19 genotyping test would be useful for determining the optimal dose of a PPI for maintenance therapy of GERD.'
ref. 16 – 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	26 patients whose GERD had healed after lansoprazole 30 mg/day for 8 weeks, 8x NM, 13x IM, 5x PM, 39% Hp-pos, received lansoprazole 15 mg/day as maintenance therapy for 6 months, co-medication unknown; NM versus IM versus PM: - Frequency of recurrence of GERD symptoms (%): 50 : 31 (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. These are the most common variant alleles in this (ethnically Japanese) population group.	
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 IM: AA # *17: AA	11 H. pylori-negative healthy volunteers, 5x *1/*1, 1x *1/*17, 1x *2/*17, 4x *1/*2, received lansoprazole 15 mg/day for 6 days. *1/*2 versus *1/*1: - No significant effect on the percentage of time with intragastric pH > 4 for 24 hours on Days 1 and 6 - Lansoprazole significantly increased the percentage of time with intragastric pH > 4 on Days 1 and 6 for *1/*2, but not for *1/*1 - Non-significant increase in AUC on Days 1 and 6 AUC ratio for *1/*2 versus *2/*17 versus *1/*1 versus *1/*17: - 1.7 : 1.3 : 1 : 0.45 (value for *1/*1 = 1.04 µg.h/ml) (NS) Note: Genotyping was performed for *2, *3, *4, *5, *6 and *17.	Authors' conclusion: 'This study showed that the acid-inhibitory effects of lansoprazole in Caucasians were influenced by CYP2C19 status. Due to this effect, single and repeated administration of lansoprazole 15 mg in *1/*1 subjects did not provide significant acid-inhibition when compared with baseline.' AUC versus NM: IM: 178%
ref 18 - GERD Sakurai Y et al. Population pharmacokinetics and proton pump inhibitory effects of intravenous lansoprazole in healthy Japanese	4	56 healthy volunteers, 16x NM, 32x IM, 8x PM, received a single dose of lansoprazole 30 mg IV. Intragastric pH was determined in 32 volunteers, 9x NM, 15x IM, 8x PM, who received lansoprazole 30 mg IV twice daily for 1 day. NM versus IM versus PM: - Mean intragastric pH on Day 1: approximately 4 : 5 (NS) : 6 (NS)	Authors' conclusion: "The present study indicates that CYP-2C19*2 and *3 alleles are responsible for the pharmacokinetic variability of intravenously administered lansopra-

males. Biol Pharm Bull 2007;30:2238-43. **ref. 18, continuation**	IM: AA PM: A	- % of time day-time pH > 4.0: 43.9 : 70.7 (NS) : 84.3 (NS) - % of time night-time pH > 4.0: 53.5 : 79.2 (NS) : 95.9 (NS) - Clearance (L.kg/h): 0.187 : 0.109 (S) : 0.039 (S) Note: Genotyping was performed for *2 and *3. These are the most common variant alleles in this (ethnically Japanese) population group.	zole among Japanese." Clearance versus NM: IM: 58% PM: 21%
ref. 19 – GERD Kawamura M et al. Cytochrome P450 2C19 polymorphism influences the preventive effect of lansoprazole on the recurrence of erosive reflux esophagitis. J Gastroenterol Hepatol 2007;22:222-6.	3 IM: AA# PM: AA#	82 patients with healed grade A-D erosive reflux oesophagitis after treatment with lansoprazole for 8 weeks, 26x NM, 41x IM, 15x PM, 26.8% Hp-pos, received lansoprazole 15 mg/day as maintenance therapy for 6 months, co-medication unknown; recurrence of reflux oesophagitis was diagnosed by endoscopy after 6 months or on recurrence of GERD symptoms. NM versus IM versus PM: - Recurrence of erosive reflux oesophagitis (%): 38.5 : 22.0 (S) : 0 (S) - Recurrence of GERD symptoms (%): 8.0 : 9.8 (NS) : 0 (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 efficacy of lansoprazole (15 mg/day) as maintenance therapy for erosive reflux esophagitis is influenced by CYP2C19 polymorphism."
ref. 20 – GERD Furuta T et al. Effect of concomitant dosing of famotidine with lansoprazole on gastric acid secretion in relation to CYP2C19 genotype status. Aliment Pharmacol Ther 2005;22:67-74.	4 PM: AA# IM: AA	20 healthy volunteers, 6x NM, 9x IM (7x *1/*2, 2x *1/*3), 5x PM (2x *2/*2, 2x *2/*3, 1x *3/*3), Hp-neg, received lansoprazole 60 mg for 7 days, no co-medication; NM versus IM versus PM: - pH on Day 7: 4.5 : 5.0 (NS) : 6.1 (S) - % of time pH > 4.0 on Day 7: only for PM > 80%; NM and IM sign. lower versus PM. Note: Genotyping was performed for *2 and *3.	
ref. 21 – GERD Kawamura M et al. The effects of lansoprazole on erosive reflux oesophagitis are influenced by CYP2C19 polymorphism. Aliment Pharmacol Ther 2003;17:965-73.	3 IM: AA# PM: AA#	88 patients with reflux oesophagitis, 31x NM, 40x IM, 17x PM, Hp-neg and Hp-pos (no sign. differences in Hp infection status between genotypes), received lansoprazole 30 mg/day for 8 weeks, co-medication unknown; NM versus IM versus PM: - Healed after 4 weeks (%): 57.1 : 69.2 (NS) : 72.7 (NS) - Healed after 8 weeks (%): 77.4 : 95.0 (S) : 100 (S) Note: Genotyping was performed for *2 and *3.	
ref. 22 – GERD Furuta T et al. Effect of cytochrome P4502C19 genotypic differences on cure rates for gastroesophageal reflux disease by lansoprazole. Clin Pharmacol Ther 2002;72:453-60.	3 IM: AA# PM: AA#	74 patients with GERD (grade A-C), 24x NM, 28x IM (19x *1/*2, 9x *1/*3), 13x PM (7x *2/*2, 6x *2/*3), received lansoprazole 30 mg for 8 weeks, co-medication unknown; NM versus IM versus PM: - Healed (%): 45.8 : 67.9 (S) : 84.6 (S) - C_{ss} lansoprazole (ng/mL): 312.3 : 439.9 (NS) : 745.4 (S) Note: Genotyping was performed for *2 and *3.	C_{ss} versus NM: IM: 141% PM: 239%
ref. 23 – GERD Shirai N et al. Comparison of lansoprazole and famotidine for gastric acid inhibition during the	4	15 healthy volunteers, 7x NM, 5x IM (4x *1/*2, 1x *1/*3), 3x PM (1x *2/*2, 2x *2/*3), Hp-neg, received lansoprazole 30 mg/day for 8 days, no co-medication; NM versus IM versus PM:	AUC versus NM: IM: 220%

day-time and night-time in different CYP2C19 genotype groups. Aliment Pharmacol Ther 2002;16:837-46.	IM: AA PM: AA#	- pH on Day 8: 4.4 : 4.9 (NS) : 5.4 (S) - AUC ratio: 1 : 2.2 (NS) : 4.6 (S) Note: Genotyping was performed for *2 and *3.	PM: 460%
ref. 24 – GERD Furuta T et al. Effect of high-dose lansoprazole on intragastric pH in subjects who are homozygous extensive metabolizers of cytochrome P450-2C19. Clin Pharmacol Ther 2001;70:484-92.	4 IM:AA# PM:AA#	18 healthy volunteers, 7x NM, 7x IM (5x *1/*2, 2x *1/*3), 4x PM (2x *2/*2, 2x *2/*3), Hp-neg, received lansoprazole 30 mg/day for 8 days, no co-medication; NM versus IM versus PM: - pH on Dag 8: IM and PM sign. increased versus NM. - pH < 4 between 22.00-06.00h (hour): 5.9 : 3.1 (S) : 2.5 (S) - AUC ratio: 1.0 : 2.41 (NS) : 5.39 (S) Note: Genotyping was performed for *2 and *3.	AUC versus NM: IM: 241% PM: 539%
ref. 25 – GERD Adachi K et al. CYP2C19 genotype status and intragastric pH during dosing with lansoprazole or rabeprazole. Aliment Pharmacol Ther 2000;14:1259-66.	3 IM:AA PM:AA#	20 healthy volunteers, 7x NM, 9x PM, 4x PM; Hp-neg, received lansoprazole 30 mg/day for 7 days, no co-medication; NM versus IM versus PM: - % night-time pH < 4: 81.5 : 70.9 (NS) : 39.5 (S)	
ref. 26 – GERD Howden CW et al. Dose-response evaluation of the antisecretory effect of continuous infusion intravenous lansoprazole regimens over 48 h. Aliment Pharmacol Ther 2006;23:975-84.	4 IM:AA	33 healthy volunteers, 23x NM, 10x IM (*1/*2 or *1/*4), Hp-neg, received a lansoprazole 60-90 mg *IV* bolus + 6-9 mg/h for 2 days, no co-medication; NM versus IM: - pH on Day 2: 4.9-5.4 : 5.7-6.1 (NS) - % time pH > 6.0: 29.0-41.8 : 40.8-71.4 (NS) - Cl (L/h): 16.5 : 9.2 (NS) Note: Genotyping was performed for *2, *3 and *4.	
ref. 27 – 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	Meta-analysis of 6 studies with triple therapy (lanso + amoxi + clari or lanso + amoxi + metro) for 1-2 weeks in Hp-positive patients who had not previously received eradication therapy. Total number of patients and distribution of genotypes was not specified. 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 also included in this risk analysis separately (Kawabata 2003; Miki 2003; Furuta, Clin Gastroenterol Hepatol 2005; Furuta, Clin Pharmacol Ther 2007). Three of the studies in this meta-analysis were also included in the meta-analysis of Padol 2006. 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-	Authors' conclusion: "The efficacy of omeprazole- and lansoprazole-based first-line triple therapies at the standard doses is dependent on CYP2C19 genotype status."

ref. 27, continuation	IM:AA[#] PM:AA[#]	dardised. Publication bias analysis was not performed. NM versus IM versus PM: - OR for eradication of Hp: 1.0 : 1.95 (95% CI 1.03-3.70) : 3.06 (95% CI 1.56-6.00)	
ref. 28 – Hp Furuta T et al. Effect of MDR1 C3435T polymorphism on cure rates of Helicobacter pylori infection by triple therapy with lansoprazole, amoxicillin and clarithromycin in relation to CYP2C19 genotypes and 23S rRNA genotypes of H. pylori. Aliment Pharmacol Ther 2007;26:693-703.	4 IM:AA[#] PM:AA[#]	313 patients, 107x NM, 152x IM, 54x PM, 71% clari-susceptible Hp, received twice daily lanso 30 mg + amoxi 750 mg + clari 200 mg for 1 week, followed by twice daily famotidine 20 mg for patients with peptic ulcers (n=165), no co-medication or alcohol; NM versus IM versus PM: - Eradication %: 66 : 79 (S) : 89 (S) - OR for eradication failure: 1.0 : 0.305 (95% CI 0.143-0.649) : 0.073 (95% CI 0.022-0.238) Note: Genotyping was performed for *2 and *3. These are the most common variant alleles in this (ethnically Japanese) population group.	Authors' conclusion: "CYP2C19 genotype is one of the determinants of successful eradication of H. pylori by the triple therapy with lansoprazole, amoxicillin and clarithromycin."
ref. 29 – Hp Sugimoto M et al. Evidence that the degree and duration of acid suppression are related to Helicobacter pylori eradication by triple therapy. Helicobacter 2007;12:317-23.	3 IM:AA[#] PM:AA[#]	32 patients, 11x NM, 13x IM, 8x PM, 79% clari-susceptible Hp, received twice daily lanso 30 mg + amoxi 750 mg + clari 400 mg for 1 week, co-medication unknown; NM versus IM versus PM: - Eradication %: 63.6 : 77.0 (NS) : 87.5 (NS) - Median pH on Day 6: 6.0 : 6.1 (NS) : 7.1 (S) - % time pH > 4.0 on Day 6: 85.6 : 99.0 (S) : 100 (S) Note: Genotyping was performed for *2 and *3. These are the most common variant alleles in this (ethnically Japanese) population group.	Authors' conclusion: "We found that the intragastric pH during the triple eradication therapy was correlated with the CYP2C19 genotype status."

ref. 30 – Hp
Furuta T et al.
Pharmacogenomics-based tailored versus standard therapeutic regimen for eradication of H. pylori.
Clin Pharmacol Ther 2007;81:521-8.
	3
	
	PM:AA[#]
	
	IM:AA[#]
		211 patients with clari-susceptible Hp, co-medication unknown.
		106 patients, 41x NM, 51x IM, 14x PM, received twice daily lanso 30 mg + amoxi 750 mg + clari 400 mg for 1 week (standard therapy).
		105 patients, 37x NM, 53x IM, 15x PM, received either 3x daily lanso 30 mg (NM) or 3x daily lanso 15 mg (IM) or twice daily lanso 15 mg (PM) + 3x daily amoxi 500 mg + 3x daily clari 200 mg for 1 week (genotype-guided therapy). The lansoprazole dose was selected for each genotype to lead to a median intragastric pH ≥ 5.0 for 24 hours.
		44 patients with clari-resistant Hp, 11x NM, 23x IM, 10x PM, received standard therapy.
		
		NM versus IM versus PM:
		- Clari-susceptible Hp:
		  - Eradication % with standard therapy (intention to treat): 73.2 : 82.4 (NS) : 100 (S)
		  - Eradication % with genotype-guided therapy (intention to treat): 100 : 94.3 (NS) : 93.3 (NS)
		- Clari-resistant Hp:
		  - Eradication % with standard therapy (intention to treat): 0.0 : 47.8 (S) : 80 (S)
		
		Genotype-guided versus standard therapy:
		- Higher eradication % for NM (S) and IM (NS)
		- No significant difference in eradication % for PM
			Authors' conclusion: "This study is the first to prove prospectively that a pharmacogenomics-based tailored strategy for the eradication of H. pylori enhanced the therapeutic effectiveness compared with the standard treatment without the aid of pharmacogenomics assessment."

ref. 30, continuation		- If based both on the CYP2C19 genotype and the Hp genotype (clari-susceptibility): higher eradication % for the overall group (S) and similar costs for eradication per patient (including second line therapy after eradication failure) Note: Genotyping was performed for *2 and *3. These are the most common variant alleles in this (ethnically Japanese) population group.	
ref. 31 – Hp Padol S et al. The effect of CYP-2C19 polymorphisms on H. pylori eradication rate in dual and triple first-line PPI therapies: a meta-analysis. Am J Gastroenterol 2006;101:1467-75.	3 IM:AA PM:AA	Meta-analysis of 5 studies with triple therapy (lanso 30 mg twice daily + amoxi + clari) for 1-2 weeks in Hp-positive patients who had not previously received eradication therapy. 333 patients (121x NM, 164x IM, 48x PM). Only studies with a Jadad quality assessment score ≥ 2 were included. One point was given for the following three parameters: randomisation, blinding (double or single blinding either to treatment or genotype groups), and dropouts/withdrawals recorded. However, the results of the quality assessments were not reported. Three of the studies in the meta-analysis were also included in this risk analysis separately (Inaba 2002; Kawabata 2003; Miki 2003). Meta-analysis was 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. Publication bias analysis was not performed. NM versus IM versus PM: - No significant differences in OR for eradication of Hp (NS)	Authors' conclusion: "H. pylori eradication treatment using lansoprazole is not affected by CYP-2C19 polymorphisms."
ref. 32 – Hp Sugimoto M et al. Influences of proinflammatory and anti-inflammatory cytokine polymorphisms on eradication rates of clarithromycin-sensitive strains of Helicobacter pylori by triple therapy. Clin Pharmacol Ther 2006;80:41-50.	3 IM:AA# PM:AA#	360 patients, 135x NM, 172x IM, 53x PM, clarithromycin-susceptible Hp, received twice daily ome 20 mg (n=90) or lanso 30 mg (n=214) or rabe 10 mg (n=56) + amoxi 750 mg + clari 400 mg for 1 week, co-medication unknown; No association between eradication percentage and PPI type, age, disease and sex. - Eradication %: 73.3% : 88.4% (S) : 94.3% (S) - OR for eradication failure: 1.0 : 0.439 (S) : 0.251 (S) Note: the IL1B-511 (cytokine) genotype influences the eradication percentage in NM patients. Note: Genotyping was performed for *2 and *3.	
ref. 33 – Hp Furuta T et al. Influence of CYP-2C19 polymorphism and Helicobacter pylori genotype determined from gastric tissue samples on response to triple therapy for H pylori infection. Clin Gastroenterol Hepatol 2005;3:564-73.	3 IM:AA# PM:AA#	142 patients, 46x NM, 69x IM (49x *1/*2, 30x *1/*3), 26x PM (18x *2/*2, 4x *2/*3, 4x *3/*3), 20.6% Hp was clari-resistant, no amoxi-resistance, received twice daily lanso 30 mg + 3x daily amoxi 500 mg + 3x daily clari 200 mg for 1 week, co-medication unknown, results for 139 patients; NM versus IM versus PM: - Eradication %: 57.8 : 88.2 (S) : 92.3 (S) - OR for eradication success: 1.0 : 5.6 (S) : 15.6 (S) - Significant difference in frequency of genotypes between the eradication success group (n=110) and the eradication failure group (n=29). Note: In addition to CYP2C19 genotype, clarithromycin-resistance status was also associated with eradication success. Note: Genotyping was performed for *2 and *3.	
ref. 34 - Hp Furuta T et al.	4	350 patients, 119x NM, 180x IM and 51x PM, 15% clari-resistant Hp, received twice daily ome 20 mg (n=175) or	

Polymorphism of interleukin-1beta affects the eradication rates of Helicobacter pylori by triple therapy. Clin Gastroenterol Hepatol 2004;2:22-30. **ref. 34, continuation**	IM:AA# PM:AA#	lanso 30 mg (n=175) + 3x daily amoxi 500 mg + 3x daily clari 200 mg for 1 week, no co-medication; NM versus IM versus PM: - Eradication % of clari-susceptible Hp: 72% : 94% : 98% (S) Note: Separate eradication percentages for lanso and ome were not given. Note: Eradication % for clari-resistant Hp was lower than for non-resistant strains. Note: IL-1β-511 genotype influenced the eradication percentage in NMs. Note: Genotyping was performed for *2 and *3.	
ref. 35 - Hp Kawabata H et al. Effect of different proton pump inhibitors, differences in CYP2C19 genotype and antibiotic resistance on the eradication rate of Helicobacter pylori infection by a 1-week regimen of proton pump inhibitor, amoxicillin and clarithromycin. Aliment Pharmacol Ther 2003;17:259-64.	3 IM:AA# PM:AA#	87 patients, 33x NM, 35x IM, 12x PM, 11% clari-resistant Hp, no amoxi resistance, received twice daily lanso 30 mg + amoxi 750 mg + clari 400 mg for 1 week, co-medication unknown; NM versus IM versus PM: - Eradication % of clari-susceptible Hp: 74% : 83% (S) : 100% (S) Note: Eradication % for clari-resistant Hp was significantly lower than for non-resistant strains. Note: Genotyping was performed for *2 and *3.	
ref. 36 – 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, 10x NM, 23x IM and 7x PM, 100% clari-susceptible Hp, no amoxi-resistance, received twice daily lanso 30 mg + amoxi 750 mg + clari 400 mg for 1 week, co-medication unknown; NM versus IM versus PM: - Eradication %: 100% : 95.7 (NS) : 100% (NS) Note: Genotyping was performed for *2 and *3.	
ref. 37 - Hp Furuta T et al. Effect of genotypic differences in CYP-2C19 on cure rates for Helicobacter pylori infection by triple therapy with a proton pump inhibitor, amoxicillin, and clarithromycin. Clin Pharmacol Ther 2001;69:158-68.	4 IM:AA# PM:AA#	271 patients, 88x NM, 127x IM (95x *1/*2, 32x *1/*3), 46x PM (26x *2/*2, 15x *2/*3, 5x *3/*3), received twice daily ome 20 mg (n=136) or lanso 30 mg (n=135) + 3x daily amoxi 500 mg + 3x daily clari 200 mg for 1 week, PPI was continued for 5-7 weeks, with co-medication; NM versus IM versus PM: - Eradication %: 72.7% : 92.1% (S) : 97.8% (S) Note: Separate eradication percentages for lanso and ome were not given. Note: Genotyping was performed for *2 and *3.	Authors' conclusion: "If the CYP2C19 genotype status is determined before treatment, an optimal dose of a PPI may be prescribable on the basis of this pharmacogenetic or pharmacogenomic status. We also strongly recommend that the doses of PPI's in …H.pylori eradication regimen should be increa-

<table>
<tr><td>ref. 37, continuation</td><td></td><td></td><td>sed, … especially in western countries…”</td></tr>
<tr><td>ref. 38 – Hp
Inaba T et al.
Helicobacter pylori infection: CYP2C19 genotype and serum ferritin.
J Gastroenterol Hepatol 2002;17:748-53.</td><td>3

IM:AA
PM:AA</td><td>58 patients, 20x NM, 29x IM, 9x PM; clari-susceptible Hp, received twice daily lanso 30 mg + 3x daily amoxi 500 mg + twice daily clari 200 mg for 1 week, co-medication unknown:

NM versus IM versus PM:
- Eradication %: 90.0% : 89.7% (NS) : 88.9% (NS)

Note: Genotyping was performed for *2 and *3.</td><td></td></tr>
<tr><td>ref. 39, kin
Qiao HL et al.
Pharmacokinetics of three proton pump inhibitors in Chinese subjects in relation to the CYP2C19 genotype.
Eur J Clin Pharmacol 2006;62:107-12.
PubMed PMID: 16402242.</td><td>3

IM: AA
PM: A</td><td>18 healthy volunteers, selected on basis of their CYP2C19 genotype, received a single dose of lansoprazole 30 mg. Co-medication was excluded.

Genotyping:
- 6x NM
- 6x IM
- 6x PM

Results:
<table><tr><td colspan="2">AUC compared to NM (3.15 µg.h/ml):</td></tr><tr><td>IM</td><td>x 1.78 (NS)</td></tr><tr><td>PM</td><td>x 4.01 (S)</td></tr></table>
Note: Genotyping was for *2 and *3. These are the most important gene variants in this Chinese population.</td><td>Authors’ conclusion: ‘The pharmacokinetic characteristics of the three PPIs are significantly dependent on the CYP-2C19 genotype status.’

AUC versus NM:
IM: 178%
PM: 401%</td></tr>
<tr><td>ref. 40, kin
Miura M et al.
Pharmacokinetic differences between the enantiomers of lansoprazole and its metabolite, 5-hydroxylansoprazole, in relation to CYP2C19 genotypes.
Eur J Clin Pharmacol 2004;60:623-8.
PubMed PMID: 15448955.</td><td>3

IM: AA
PM: A</td><td>18 healthy volunteers, selected on basis of their CYP2C19 genotype, received a single dose of lansoprazole 60 mg. Exclusion of co-medication was not mentioned. Smoking, alcohol and caffeine were excluded.

Genotyping:
- 6x NM
- 6x IM
- 6x PM

Results:
<table><tr><td colspan="2">AUC compared to NM (5.53 µg.h/ml):</td></tr><tr><td>IM</td><td>x 1.49 (NS)</td></tr><tr><td>PM</td><td>x 4.34 (S)</td></tr></table>
Note: Genotyping was for *2 and *3. These are the most important gene variants in this Japanese population.</td><td>Authors’ conclusion: ‘The pharmacokinetic outcomes of lansoprazole enantiomers were significantly different among the three genotype groups.’

AUC versus NM:
IM: 149%
PM: 434%</td></tr>
<tr><td>ref. 41, kin
Hu YR et al.
Pharmacokinetics of lansoprazole in Chinese healthy subjects in relation to CYP2C19 genotypes.
Acta Pharmacol Sin 2004;25:986-90.
PubMed PMID: 15301728.</td><td>3

PM: A</td><td>18 healthy volunteers, selected on basis of their CYP2C19 genotype, received a single dose of lansoprazole 30 mg. Co-medication was excluded.

Genotyping:
- 9x NM
- 9x PM

Results:
<table><tr><td colspan="2">AUC compared to NM (3.23 µg.h/ml):</td></tr><tr><td>PM</td><td>x 3.42 (S)</td></tr></table>
Note: Genotyping was for *2 and *3. These are the most important gene variants in this Chinese population.</td><td>Authors’ conclusion: ‘CYP2C19 genotype is the major factor to influence the inter-individual kinetic variability of lansoprazole.’

AUC versus NM:
PM: 342%</td></tr>
<tr><td>ref. 42, kin
Ieiri I et al.
Comparison of the kinetic disposition of and serum gastrin</td><td>4</td><td>15 healthy volunteers, selected on basis of their CYP2C19 genotype, received lansoprazole 30 mg once daily for 8 days.
Co-medication was excluded.</td><td>Authors’ conclusion: ‘The disposition kinetic behaviour of the two PPIs is co-segregated with</td></tr>
</table>

<table>
<tr>
<td>change by lansoprazole versus rabeprazole during an 8-day dosing scheme in relation to CYP2C19 polymorphism.
Eur J Clin Pharmacol
2001;57:485-92.
PubMed PMID:
11699613.

ref. 42, continuation</td>
<td>PM: A
IM: AA</td>
<td>Genotyping:
- 5x NM
- 5x IM
- 5x PM

Results:
<table>
<tr><td colspan="4">AUC compared to NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>value for NM</td></tr>
<tr><td>day 1</td><td>x 5.55 (S)</td><td>x 1.80 (NS)</td><td>2.0 µg.h/ml</td></tr>
<tr><td>day 8</td><td>x 3.88 (S)</td><td>x 1.71 (NS)</td><td>1.7 µg.h/ml</td></tr>
<tr><td colspan="4">For all genotype groups the AUC at day 8 was smaller than the AUC at day 1, but the difference was only significant for PM.
These data show that lansoprazole does not inhibit its own metabolism (CYP2C19 and CYP3A4).</td></tr>
</table>

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

AUC versus NM:
IM: 175%
PM: 472%</td>
</tr>
<tr>
<td>ref. 43, kin
Sakai T et al.
CYP2C19 genotype and pharmacokinetics of three proton pump inhibitors in healthy subjects.
Pharm Res
2001;18:721-7.
PubMed PMID:
11474773.</td>
<td>3

IM: AA
PM: A</td>
<td>18 healthy volunteers, selected on basis of their CYP2C19 genotype, received a single dose of lansoprazole 30 mg. Co-medication and alcohol were excluded.

Genotyping:
- 6x NM
- 6x IM
- 6x PM

Results:
<table>
<tr><td colspan="2">AUC compared to NM (2.55 µg.h/ml):</td></tr>
<tr><td>IM</td><td>x 1.37 (NS)</td></tr>
<tr><td>PM</td><td>x 3.68 (S)</td></tr>
</table>

Note: Genotyping was for *2 and *3. These are the most important gene variants in this Japanese population.</td>
<td>Authors’ conclusion: ‘Pharmacokinetic profiles of omeprazole and lansoprazole were well correlated with the CYP-2C19 genotype.’

AUC versus NM:
IM: 137%
PM: 368%</td>
</tr>
<tr>
<td>ref. 44, kin
Katsuki H et al.
Genetic polymorphism of CYP2C19 and lansoprazole pharmacokinetics in Japanese subjects.
Eur J Clin Pharmacol
1997;52:391-6.
PubMed PMID:
9272410.</td>
<td>3

IM: AA
PM: A</td>
<td>8 healthy volunteers, selected on basis of their CYP2C19 genotype, received a single dose of lansoprazole 30 mg. Co-medication was excluded.

Genotyping:
- 3x NM
- 2x IM
- 3x PM

Results:
<table>
<tr><td colspan="2">Cl_{or} compared to NM (3.77 ml/min.kg):</td></tr>
<tr><td>IM</td><td>x 0.47 (NS)</td></tr>
<tr><td>PM</td><td>x 0.21 (S for PM versus NM+IM)</td></tr>
<tr><td colspan="2">There was a large difference in the mean weight of PM versus NM (49 versus 63 kg) (significance not determined). The volunteers with the 3 lowest body weights were all PM.</td></tr>
</table>

Note: Genotyping was for *2 and *3. These are the most important gene variants in this Japanese population.</td>
<td>Authors’ conclusion: ‘The hydroxylation of lansoprazole to 5-hydroxylansoprazole was apparently impaired in the subjects with the genetic defects of CYP2C19 (m1/m1 or m1/m2).’

Cl_{or} versus NM:
IM: 47%
PM: 21%</td>
</tr>
<tr>
<td>ref. 45
SmPC Lansoprazole Mylan 16-12-22.</td>
<td>0

PM: A</td>
<td><u>CYP2C19 poor metabolisers</u>:
CYP2C19 is subject to genetic polymorphism and 2-6%- the poor metabolisers (PM), are homozygous for a mutated CYP2C19 allele, and therefore do not have a functional CYP2C19 enzyme Exposure in poor metabolisers is many times higher than in normal metabolisers.</td>
<td></td>
</tr>
<tr>
<td>ref. 46
SmPC Prezal (lan-</td>
<td>0</td>
<td><u>Drug interactions</u>:
Tacrolimus. Clinical Impact: Potentially increased exposure</td>
<td></td>
</tr>
</table>

soprazole), USA, 08-08-23.	IM: AA PM: AA	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 purpose of classification of the severity of the effect is to classify negative effects, code AA is used for a positive effect.

Risk group	UM with inducers of CYP2C19 and/or CYP3A4

Comments:

- Of the articles on efficacy published after 2009, only articles were included with data on patients with the *17-variant or with data on more than 200 patients.
  Only kinetic studies were included with oral administration, data on AUC, steady state concentration or clearance in comparison with NMs and with data on more than 1 PM or on patients with the *17-variant.
  Other studies did not add enough to the evidence to be included.
  Studies with eradication therapy based on two or four medicines were not included in the status report, nor studies in which the dose of the PPI was lower than the dose registered for eradication in the Netherlands.
- GERD
  Furuta T et al. Pharmacogenomics 2004;5:181-202:
  "There is evidence of reduced clearance with repeated administrations of PPIs resulting in more profound acid suppression. Therefore, observations after single dose administration cannot be extrapolated to more long-term use." "Although the differences among the various genotypes become smaller with longer duration of use of the PPI, they do not completely disappear." Comment KNMP Medicine Information Centre: this contradicts the Velthuyzen Van Zanten response to the meta-analysis by Padol, see below. The effect appears to be dependent on the PPI. Hunfeld et al., 2010 found an increase in the esomeprazole AUC from Day 1 to Day 5, which was similar for 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/dosing recommendations**:
  - 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 lansoprazole. CPIC states that the evidence associating CYP2C19 genotype with lansoprazole 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 B et al. CYP2C19 polymorphism affects single-dose pharmacokinetics of oral pantoprazole in healthy volunteers. Eur J Clin Pharmacol 2012;68:1267-74). 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 CYP2C19 *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 CYP2C19 *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 W-Y 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, and 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). 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 CYP2C19*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 lansoprazole 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 GL et al. Single-dose pharmacokinetics of oral and intravenous pantoprazole in children and adolescents. J Clin Pharmacol 2008;48: 1356-65). 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 2013). 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 9-7-2024, there was not a more recent version of the recommendations present on the CPIC-site.

- Furuta T et al. Effect of high-dose lansoprazole on intragastric pH in subjects who are homozygous extensive metabolizers of cytochrome P450-2C19. Clin Pharmacol Ther 2001;70:484-92. PubMed PMID: 11719736.

The authors indicate that doses of 30 mg four times daily are sufficient for inhibiting acid secretion during both the daytime and the night time in Japanese NMs.
The study compared intragastric pH after dosing of 30 mg once daily and 30 mg four times daily for 8 days in 5 NM.

- Ward MB, Foster DJ. CYP2C19-guided design of a proton pump inhibitor dose regimen to avoid the need for pharmacogenetic individualization in H. pylori eradication. Eur J Clin Pharmacol 2011;67:261-6. PubMed PMID: 21079935.
  Utilising pharmacokinetic modelling, the authors found an optimal dose for eradication of Helicobacter pylori of 180 mg twice daily for NM and IM, so a six times higher dose than the standard dose of 30 mg twice daily, which is the optimal dose for PM. The authors indicate that this higher dose might be given to all patients (including PM) without problems. The higher dose results in an increase of the AUC with a factor of 6, but an increase in C_{max} with only a factor of 2.5. In addition, the treatment duration for eradiction of Helicobacter pylori is only one week and lantoprazole causes few side effects.
  The authors calculated the mean and variability of the primary pharmacokinetic parameters apparent oral clearance (Cl_{or} or Cl/F), apparent volume of distribution (Vd/F) and absorption rate constant (k_a) from the AUC, C_{max} and t_{max} reported in four kinetic studies (Hu 2004; Qiao 2006; Saito M et al. Effects of clarithromycin on lansoprazole pharmacokinetics between CYP2C19 genotypes. Br J Clin Pharmacol 2005;59:302-9. PubMed PMID: 15752376; Niioka T et al. Identification of a single time-point for plasma lansoprazole measurement that adequately reflects area under the concentration-time curve. Ther Drug Monit 2006;28:321-5. PubMed PMID: 16778714). Two of these studies also examined pharmacokinetics after clarithromycin co-administration (Saito 2005 and Niioka 2006). Clarithromycin inhibits CYP3A4/5, which has a stronger effect on the pharmacokinetics in CYP2C19 PM than in NM and IM, because the lansoprazole metabolism in CYP2C19 PM is more dependent on CYP3A4/5. With these primary pharmacokinetic parameters they simulated concentration-time profiles with different doses for 7 days. The Cl_{or} calculated for NM and IM was 6.1 times that calculated for PM (8.6 versus 1.4 L/h).

- **Cost-effectiveness**:
  - Zhang Z et al. Cost-utility analysis of CYP2C19 genotype detection for selection of acid-suppressive therapy with lansoprazole or vonoprazan for patients with reflux esophagitis in China. Clin Drug Investig 2022;42:839-51. PMID: 35994227.
    For Chinese patients with reflux oesophagitis, CYP2C19 genotype-guided strategy and vonoprazan for all were not cost-effective regimens compared with lansoprazole for all at a willingness-to-pay threshold of 215,484 yuan (threefold the per capita gross domestic product) per quality-adjusted life-year (QALY). Additional cost per QALY were 349,627.5000 yuan and 222,387.1316 yuan, respectively. However, CYP2C19 genotype-guided therapy was the preferred regimen when vonoprazan costs decline by 40%. In addition, in the subgroup with severe reflux oesophagitis (LA Grade C/D according to the Los Angeles Classification), CYP2C19 genotype-guided therapy and vonoprazan for all were cost-effective compared with lansoprazole for all at 56920.8131 yuan/QALY and 9016.9727 yuan/QALY, respectively, considerably below the onetime gross domestic product per capita. Genotype-guided treatment consisted of lansoprazole for PM and vonoprazan (which is not available in the Netherlands) for NM and IM.
    Varying all input parameters showed a 8.30% probability that genotyping was cost-effective and a 46.20% probability that vonoprazan for all was cost-effective for the whole group of Chinese patients with reflux oesophagitis. Direct medical costs (medication costs (initial treatment and maintenance treatment with lansoprazole and vonoprazan), CYP2C19 genetic testing costs, endoscopy costs, and the physical examination costs during the follow-up visits), direct non-medical costs (follow-up visit-related transportation expenses and meal fees) and indirect costs (loss of work productivity) were calculated over a period of 1 year and from a societal perspective. Patients initially received a 4-week treatment (with lansoprazole 30 mg/day or vonoprazan 20 mg/day). After that, the cured patients received half-dose maintenance treatment with no required follow-up visits, whereas the unhealed patients received retreatment for 4 weeks and follow-up visits with a complete physical examination and conventional endoscopy. After an 8-week treatment period, the healed patients remained as mentioned above, the unhealed patients and those with a recurrence were treated again with the same initial treatment. For 1000 patients, lansoprazole for all resulted in total costs of 1152.0356 yuan and a gain of 0.7145 QALYs. Genotype-guided therapy resulted in total costs of 2480.6201 yuan and a gain of 0.7183 QALYs. Thus genotype-guided therapy resulted in additional costs of 1328.5845 yuan for an additional gain of 0.0038 QALYs. Vonoprazan for all resulted in total costs of 1997.1067 yuan and a gain of 0.7183 QALYs. In the subgroup with severe oesophagitis, lansoprazole for all resulted in total costs of 2148.0766 yuan and a gain of 0.7051 QALYs, genotype-guided therapy resulted in total costs of 2757.1293 yuan and 0.7183 QALYs, and vonoprazan for all resulted in total costs of 2247.2633 yuan and 0.7161 QALYs. Costs included in the calculation were lansoprazole costs of 3.09 yuan for 30 mg and 1.57 yuan for 15 mg, vonoprazan costs of 9.90 yuan for 20 mg and 4.95 yuan for 10 mg, endoscopy costs of 796.87 yuan, physical examinations costs of 19.83 yuan, costs of work loss of 373.10 yuan, costs of transport and meal expenses of 73.99 yuan, and costs of 720.00 yuan for the genotyping test. The CYP2C19 genotype distribution was derived from a Japanese study where the proportion of NM+IM and PM was 80.70% and 19.30%, respectively, which was consistent with a previous report on the Asian population, Transition probabilities were derived from two Japanese clinical trials, including healing rates and recurrence rates on universal medication strategies and on the optimized treatment of different CYP2C19 genotype subgroups (Ashida K et al. Randomised clinical trial: vonoprazan, a novel potassium-competitive acid blocker, vs. lansoprazole for the healing of erosive

oesophagitis. Aliment Pharmacol Ther 2016;43:240-51 and Ashida K et al. Maintenance for healed erosive esophagitis: phase III comparison of vonoprazan with lansoprazole. World J Gastroenterol 2018;24:1550-61).

Date of literature search: 17 June 2024.

	Phenotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	IM	4 C	Yes	No	10 September 2024
	PM	4 C	Yes	No	
	UM	--	Yes	Yes	

Mechanism:
Lansoprazole is primarily converted by CYP2C19 and CYP3A4/5 to inactive metabolites (respectively 5'-hydroxy lansoprazole and lansoprazole sulphone). Reduced CYP2C19 activity results in higher plasma concentrations and a higher lansoprazole AUC and can therefore result in improved therapeutic effectiveness and/or a higher incidence of side effects. The extent and duration of effective acid inhibition by proton pump inhibitors is dependent on the AUC.

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