CYP2C19-Proton Pump Inhibitor Evidence Summary

Drug (Evidence Level)*	FDA Label or PGx Guidelines	Comments
Omeprazole (2A)	FDA Label: In EMs, omeprazole is primarily metabolized by CYP2C19. The systemic exposure to omeprazole varies with a patient's metabolism status: PM > IM > EM.+ DPWG: ↑ dose by 100-200% in UMs[1]	• Rx and OTC • Sugimoto et al (2014): ↓ median gastric pH in EMs; greater gastric acid inhibition in PMs in 183 Japanese patients[1] • Furuta et al (1998) and Aoyama et al (1999): Higher *H. pylori* eradication rates in a total of 148 Japanese PMs[2, 3] • Tang et al (2013 meta-analysis): Lower H. pylori cure rate in Asian patients treated with omeprazole-based triple therapy in EMs vs. PMs/IMs but not IMs vs PMs[4]
Esomeprazole (3)	FDA Label: At steady state, the ratio of AUC in PMs to AUC in EMs is approximately 2.+ DPWG: ↑ dose by 50-100% in UMs[1]	• Rx and OTC • Tang et al (2013 meta-analysis): Sub-study showed no difference in *H. pylori* eradication rates with esomeprazole among Asian EMs, PMs, or IMs[4]
Pantoprazole (3)	FDA Label Adults: No dosage adjustment needed in PMs.+ FDA Label Peds: PMs have approximately 10-fold lower oral clearance vs. EMs. Consider dose reduction in known PMs.+ DPWG: ↑ dose by 400% in UMs[1]	• Rx only
Lansoprazole (2A)	FDA Label: Potential increased exposure of tacrolimus, esp in transplant patients who are CYP2C19 IMs or PMs.+ DPWG: ↑ dose by 200% in UMs[1]	• Rx and OTC • Sugimoto et al (2014): ↓ median gastric pH in EMs; greater gastric acid inhibition in PMs in 183 Japanese patients[1] • Tang et al (2013 meta-analysis): Lower H. pylori cure rate in Asian patients with lansoprazole-based triple therapy in EMs vs. PMs/IMs but not IMs vs PMs[4] • Kawamura et al (2003): Higher 4- and 8-week healing rates of GERD in PM vs. EMs in 88 Japanese patients[5] • Lima et al (2013): Post-hoc analysis of RCT data (n=271) showed increased URI or sore throat in pediatric PMs vs. EMs in the U.S.[6]
Rabeprazole (2A)	FDA label: gastric acid suppression better in PMs vs. EMs. This could be due to higher rabeprazole plasma levels in poor metabolizers.+ DPWG: No recommendations	• Rx only • Sugimoto et al (2014): ↓ median gastric pH in EMs; greater gastric acid inhibition in PMs in 183 Japanese patients[1] • Tang et al (2013 meta-analysis): Sub-study showed no difference in *H. pylori* eradication rates with rabeprazole among Asian EMs, PMs, or IMs[4]
Dexlansoprazole (N/A)	FDA label: Systemic exposure of dexlansoprazole generally higher in IMs and PMs. Mean Cmax and AUC values up to 2-fold higher in IMs compared to EMs; in PMs, mean Cmax was up to 4x higher and mean AUC up to 12x higher compared to EMs.+	• Rx only

*Evidence level as defined by PharmGKB; +Clinical Pharmacology section of FDA label unless otherwise indicated; DPWG = Dutch Pharmacogenetics Working Group; EM=Extensive metabolizer; IM=Intermediate metabolizer; PM=Poor metabolizer; UM=Ultra-rapid metabolizer; URI= Upper respiratory infection

Summary of Published Genotype-Guided Dosing Recommendations

Source	PPI	UM and/or RM	NM	IM	PM
Current PPI Protocol	**All**	**UM: ↑ dose by 100%** **RM: ↑ dose by 50%**	**--**	**↓ dose by 25%**	**↓ dose by 50%**
Lima J et al[6]	All	UM: ↑ dose by 100% RM: ↑ dose by 50%	--	↓ dose by 60%	↓ dose by 60%
DPWG[7]	Omeprazole	↑ dose by 100-200%	--	--	--
	Esomeprazole	↑ dose by 50-100%	--	--	--
	Pantoprazole	↑ dose by 400%	--	--	--
	Lansoprazole	↑ dose by 200%	--	--	--
	Dexlansoprazole	--	--	--	--
	Rabeprazole	--	--	--	--
Furuta et al[8]	All	--	--	↓ dose by 50%	↓ dose by 75%

DPWG = Dutch Pharmacogenetics Working Group; NM=Extensive metabolizer; IM=Intermediate metabolizer; PM=Poor metabolizer; UM=Ultrarapid metabolizer; RM = rapid metabolizer

CYP2C19-PPI Dosing Recommendations – UF Health PMP

CYP2C19 Phenotype	Clinical Recommendation
Rapid (e.g., **1/*17*) Ultrarapid Metabolizer (e.g., **17/*17*)	Increase dose by 50% to 100%
Normal Metabolizer (e.g., **1/*1*)	No change
Intermediate Metabolizer (e.g., **1/*2, *1/*3*) Poor Metabolizer (e.g., *2/*2, *2/*3, *3/*3)	Decrease dose by 25% to 50%

References:

1. Sugimoto M et al. Comparison of acid inhibition with standard dosages of proton pump inhibitors in relation to CYP2C19 genotype in Japanese. Eur J Clin Pharmacol. 2014; 70:1073-8.
2. Furuta T et al. Effect of genetic differences in omeprazole metabolism on cure rates for Hellocobacter pylori infection and peptic ulcer. Ann Intern Med. 1998;129:1027-30.
3. Aoyama N et al. Sufficient effect of 1-week omeprazole and amoxicillin dual treatment for Hlicobacter pylori eradication in CYP2C19 poor metabolizers. J Gastroenterol. 1999; 34(Suppl. 11), 80-83.
4. Tang H-L 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. Heimesaat MM, ed. PLoS ONE. 2013;8(4).
5. Kawamura M et al. The effects of lansoprazole on erosive reflux oesophagitis are influenced by CYP2C19 polymorphism. Aliment Pharmacol Ther. 2003;17:5-73.
6. Lima JJ et al. Association of CYP2C19 polymorphisms and lansoprazole associated respiratory adverse effects in children. J Pediatr. 2013;63:686-91.
7. Swen JJ et al. Pharmacogenetics: from bench to byte--an update of guidelines. Clin Pharmacol Ther. 2011;89:662-73.
8. Furuta T et al. Individualized therapy for gastroesophageal reflux disease: potential impact of pharmacogenetic testing based on CYP2C19. Mol Diagn Ther. 2012;16:223-34.