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Omeprazole Therapy and *CYP2C19* Genotype

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Introduction

Omeprazole (brand name Prilosec) is a first-generation proton pump inhibitor (PPI) used to treat gastroesophageal reflux disease (GERD), gastric ulcers, duodenal ulcers, upper gastrointestinal (GI) tract inflammatory conditions, eosinophilic esophagitis, and erosive esophagitis. Omeprazole is also used in the treatment of hypersecretory conditions, such as Zollinger-Ellison syndrome, and is used with antibiotics to eradicate *Helicobacter pylori (H. pylori)*.

Omeprazole reduces the acidity (raises the pH) in the stomach by inhibiting the secretion of gastric acid. The level of individual omeprazole exposure is influenced by several factors, such as the dose administered, amount of drug absorbed, as well as the kinetics of drug metabolism and drug inactivation.

Omeprazole is primarily metabolized by the CYP2C19 enzyme. Individuals with increased CYP2C19 enzyme activity ("CYP2C19 rapid and ultrarapid metabolizers") may have an insufficient response to standard doses of omeprazole because the drug is inactivated at a faster rate. In contrast, individuals who have reduced or absent CYP2C19 enzyme activity (namely, CYP2C19 intermediate and poor metabolizers) have greater plasma concentrations of omeprazole, which is associated with more potent acid suppression. The frequencies of CYP2C19 metabolizer phenotypes vary among global populations.

The FDA-approved drug label does not give dosing guidance for CYP2C19 intermediate or ultrarapid metabolizers (1) (Table 1); however, it does recommend a reduced dosage for individuals of Asian descent without regard for CYP2C19 metabolizer status. It is important to note that early PPI research studies investigating the *CYP2C19* gene were conducted in Asian populations with ultrarapid and rapid metabolizer phenotypes making up only 1.3–4% of Asian populations compared with approximately 20% of non-Asian populations.

In 2018, PPI dosing recommendations for all *CYP2C19* metabolizer phenotypes were published by the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP) (Table 2) (2, 3). For poor and intermediate metabolizers, DPWG recommends no alteration in dosing based on their consensus that higher plasma concentration of omeprazole results in an increase in the therapeutic effectiveness without an increase in side effects. For CYP2C19 ultrarapid metabolizers with *H. pylori* infection, DPWG states that the dose of omeprazole should be increased 3-fold for the eradication of infection. For other indications (for example, GERD), the physician should be aware of possible reduced effectiveness if

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individuals are rapid or ultrarapid metabolizers and consider increasing the dose 3-fold. The CYP2C19 ultrarapid metabolizers should also be advised to contact their doctor if symptoms of dyspepsia persist.

In 2020, the Clinical Pharmacogenetics Implementation Consortium (CPIC) evaluated additional data and now recommends that CYP2C19 ultrarapid and rapid metabolizers may require increased doses of omeprazole to achieve desired therapeutic outcomes, whereas CYP2C19 intermediate and poor metabolizers may require reduced dosage for chronic therapy once efficacy has been established (Table 3) (4).

Table 1. The FDA Drug Label for Omeprazole: *CYP2C19* Pharmacogenomics (2020)

Phenotype	Omeprazole exposure
CYP2C19 metabolism	The systemic exposure to omeprazole varies with an individual's metabolism status: poor metabolizers > intermediate metabolizers > normal metabolizers. Approximately 3% of Caucasians and 15–20% of Asians are CYP2C19 poor metabolizers. In studies of healthy subjects, Asians had approximately a four-fold higher exposure than Caucasians. Dosage reduction of Omeprazole delayed-release capsules to 10 mg once daily is recommended for Asian individuals for maintenance of healing of erosive esophagitis.

Please see Therapeutic Recommendations based on Genotype for more information from FDA. This FDA table is adapted from (1).

Table 2. The DPWG Recommendations for Omeprazole and *CYP2C19* Genotype (2018)

Phenotype	Action	Pharmacist text
CYP2C19 poor metabolizer	No action is required for this gene-drug interaction.	The higher plasma concentration of omeprazole results in an increase in the therapeutic effectiveness, without an increase in the side effects.
CYP2C19 intermediate metabolizer	No action is required for this gene-drug interaction.	The higher plasma concentration of omeprazole results in an increase in the therapeutic effectiveness, without an increase in the side effects.
CYP2C19 ultrarapid metabolizer	For *Helicobacter pylori* eradication therapy: • use a 3-fold higher dose • advise the individual to report persisting symptoms of dyspepsia	The genetic variation may lead to a reduced omeprazole plasma concentration and therefore reduced effectiveness.
	Other indications • be alerted to reduced effectiveness • if necessary, use a 3-fold higher dose • advise the individual to contact their doctor if symptoms of dyspepsia persist	

Please see Therapeutic Recommendations based on Genotype for more information from DPWG. This Dutch Pharmacogenetics Working Group (DPWG) table is adapted from (2).

Table 3. The CPIC Dosing Recommendations for Omeprazole based on CYP2C19 Phenotype (2020)

CYP2C19 phenotype[a]	Implications for phenotypic measures	Therapeutic recommendation	Classification of recommendation[b]
CYP2C19 ultrarapid metabolizer	Decreased plasma concentrations of PPIs compared with CYP2C19 NMs; increased risk of therapeutic failure	Increase starting daily dose by 100%. Daily dose may be given in divided doses. Monitor for efficacy.	Optional

Table 3. continued from previous page.

CYP2C19 phenotype[a]	Implications for phenotypic measures	Therapeutic recommendation	Classification of recommendation[b]
CYP2C19 rapid metabolizer	Decreased plasma concentrations of PPIs compared with CYP2C19 NMs; increased risk of therapeutic failure	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
CYP2C19 normal metabolizer	Normal PPI metabolism: may be at increased risk of therapeutic failure compared with CYP2C19 IMs and PMs	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
CYP2C19 likely intermediate metabolizer	Likely increased plasma concentration of PPI compared with CYP2C19 NMs; likely increased chance of efficacy and potential toxicity	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[c]
CYP2C19 intermediate metabolizer	Increased plasma concentration of PPI compared with CYP2C19 NMs; increased chance of efficacy and potential toxicity	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
CYP2C19 likely poor metabolizer	Likely increased plasma concentration of PPI compared with CYP2C19 NMs; likely increased chance of efficacy and potential toxicity	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[c]
CYP2C19 poor metabolizer	Increased plasma concentration of PPI compared with CYP2C19 NMs; increased chance of efficacy and potential toxicity	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

Table adapted from (4).
IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; PPI, proton pump inhibitor *H. pylori*, *Helicobacter pylori*.
[a] The online *CYP2C19* Frequency Table provides phenotype frequencies for major race/ethnic groups, and the online *CYP2C19* Diplotype-Phenotype Table provides a complete list of possible diplotype and phenotype assignments (3, 4).
[b] Rating scheme described in the Supplemental Material online.
[c] The strength of recommendation for "likely" phenotypes are the same as their respective confirmed phenotypes. "Likely" indicates the uncertainty in the phenotype assignment, but it is reasonable to apply the recommendation for the confirmed phenotype to the corresponding "likely" phenotype.

Drug class: Proton Pump Inhibitors

Proton pump inhibitors block the secretion of gastric acid through irreversible inhibition of the H+-K+ ATPase on gastric parietal cells. They are among the most prescribed drugs in the US and globally, and some PPI formulations are available without a prescription.

According to FDA labeling, PPIs can be used to treat several conditions in adults:

- Peptic ulcer disease, including gastric and duodenal ulcers
- Eradication of *H. pylori* infection (in combination with antibiotics)

- Hypersecretory conditions (for example, Zollinger-Ellison syndrome)

According to FDA labeling, PPIs are also used in children and adults to treat:

- Symptomatic GERD
- Complications of GERD, including erosive esophagitis, peptic stricture, Barrett's esophagus
- Eosinophilic esophagitis (along with other therapeutic interventions)

Additional off-label indications for PPIs in infants, children and adults to treat:

- Acute and chronic GERD
- Acute and chronic eosinophilic esophagitis
- Acute and chronic upper GI tract inflammatory conditions

The human stomach contains approximately one billion parietal cells that secrete hydrochloric acid into the stomach (gastric lumen). Gastric acid aids digestion by hydrolyzing dietary protein and facilitating the absorption of calcium, iron, and vitamin B12. Gastric acid is also relevant to maintaining normal gastric microbiota diversity (5).

Hydrogen ions (H+) are actively secreted into the gastric lumen in exchange for potassium ions (K+) via an H^+/K^+-ATPase, which is also known as a "proton pump". Located on the luminal surface of gastric parietal cells, the proton pump controls the last step in acid secretion. The PPIs potently suppress gastric acid secretion by covalently binding to and irreversibly inactivating this proton pump.

Six PPIs are FDA-approved for clinical use in the US: esomeprazole (brand name Nexium), dexlansoprazole (Dexilant, Kapidex), lansoprazole (Prevacid), omeprazole (Prilosec), pantoprazole (Protonix), and rabeprazole (Aciphex). All PPIs are similarly potent at inhibiting gastric acid secretion and are thought to be similarly efficacious (6, 7). The available PPIs are generally grouped by first-generation (omeprazole, pantoprazole, lansoprazole) and second-generation designations (esomeprazole, dexlansoprazole, rabeprazole).

In adults, PPIs are used in the treatment of ulcers (gastric and duodenal), GERD, and to maintain healing of erosive esophagitis. Omeprazole is also used in the long-term treatment of hypersecretory conditions such as Zollinger-Ellison syndrome, multiple endocrine adenomas, and systemic mastocytosis. In children age 2 and over, omeprazole is used in the treatment of GERD and erosive esophagitis. Importantly, although FDA labeling for PPIs may have some variation, in clinical practice, PPIs are often used interchangeably and commonly for non-FDA labeled conditions such as eosinophilic esophagitis.

There are a few differences between the FDA-approved indications of different PPIs. For example, for the treatment of GERD in young children, only esomeprazole is indicated for infants from one month old (lansoprazole is licensed from one year of age, omeprazole and dexlansoprazole from 2 years of age, and rabeprazole from age 12) (8).

Nearly all PPIs, to varying degrees, are metabolized and inactivated by CYP2C19 (and to a lesser extent by CYP3A4). Additionally, given that PPIs are also inhibitors of CYP2C19 and that CYP2C19 is involved in the metabolism of many drugs, PPI administration can lead to clinically significant drug interactions. For example, the concomitant use of a PPI and clopidogrel, which requires CYP2C19 for bioactivation, has been associated with reduced antiplatelet activity, indicating that the concurrent administration of omeprazole with clopidogrel must balance overall risks and benefits, considering both cardiovascular and GI complications (9, 10, 11, 12, 13). The FDA specifically addresses interactions between omeprazole and multiple drugs that interact with CYP2C19 and CYP3A4 (including St. John's Wort or rifampin). These drug-drug interactions may result in altered drug exposure for all CYP2C19 substrate medications (1).

Genetic variation in the *CYP2C19* gene influences the clearance of PPIs that may in turn, influence treatment outcomes. First-generation PPIs (omeprazole, lansoprazole, and pantoprazole) and second-generation

dexlansopraozle are dependent on CYP2C19 metabolism. In contrast, second-generation PPIs of esomeprazole and rabeprazole are less likely to be influenced by *CYP2C19* genotype (14, 15, 16, 17).

Drug: Omeprazole

Omeprazole was the first PPI to be introduced to the US market in 1989. Today, omeprazole is one of the PPIs that are available both as prescription and over-the-counter medications.

Omeprazole is metabolized and inactivated in the liver by the cytochrome P450 system. The CYP2C19 enzyme is the principal enzyme involved, although other enzymes such as CYP3A4 also contribute to a lesser degree. Omeprazole is metabolized to hydroxy and desmethyl metabolites, which is thought to have no effect on gastric acid secretion.

The long-term use of PPIs has been associated with some adverse effects, which may include but are not limited to infections, kidney disease, bone fractures and electrolyte disturbances. Many of these may stem from longstanding hypochlorhydria/achlorhydria, including B12 deficiency or iron deficiency. There can also be an increased risk of enteric infections, including *Salmonella*, *Campylobacter*, and the vegetative form of *Clostridium difficile* (17). There are mixed data from large epidemiological studies of the association with PPIs and other adverse outcomes, but these have largely not been substantiated and instead may represent residual confounding. Nevertheless, as with most drugs, the lowest effective dose for the shortest duration appropriate to the condition is applicable to PPIs. (1) Notably, there are only a few clinical diseases, such as Barrett's esophagus with dysplasia, that necessitate chronic PPI use.

Studies have not adequately assessed the safety of omeprazole therapy during pregnancy. Epidemiology studies failed to find an increased risk of major congenital malformations or other adverse pregnancy outcomes when omeprazole was used during pregnancy.

Gene: *CYP2C19*

The CYP superfamily is a large and diverse group of hepatic enzymes that form the major system for metabolizing lipids, hormones, toxins, and drugs. The CYP genes are very polymorphic and can result in reduced, absent, or increased drug metabolism.

The CYP2C19 enzyme contributes to the metabolism of a range of clinically important drugs, including antidepressants, antiplatelet agents, anti-fungal agents, some proton pump inhibitors, and benzodiazepines such as diazepam.

The *CYP2C19* gene is highly polymorphic, as there are over 35 variant star (*) alleles cataloged by the Pharmacogene Variation (PharmVar) Consortium. The *CYP2C19*1* is considered the wild-type allele when no variants are detected and is associated with normal enzyme activity and the "normal metabolizer" phenotype.

The *CYP2C19*17* allele is associated with increased enzyme activity and is found among individuals with 'rapid' (**1/*17*) and 'ultrarapid' (**17/*17*) metabolizer phenotypes. Individuals who have one copy of non-functional alleles (for example, **2* and **3*) are classified as 'intermediate metabolizers' (for example, **1/*2*), and individuals who have 2 non-functional alleles are classified as "poor metabolizers" (for example, **2/*2*, **2/*3*) (Table 4).

Table 4. The CPIC Assignment of *CYP2C19* Phenotype based on Genotype (2017)

Phenotype	Genotype	Examples of diplotype
CYP2C19 ultrarapid metabolizer (approximately 2–5% of individuals)[a]	An individual with 2 increased function alleles	**17/*17*
CYP2C19 rapid metabolizer (approximately 2–30% of individuals)	An individual with one normal function allele and one increased function allele	**1/*17*

Table 4. continued from previous page.

Phenotype	Genotype	Examples of diplotype
CYP2C19 normal metabolizer (approximately 35–50% of individuals)	An individual with 2 normal function alleles	**1/*1*
CYP2C19 intermediate metabolizer (approximately 18–45% of individuals)	An individual with one normal function allele and one no function allele or one no function allele and one increased function allele	**1/*2* **1/*3* **2/*17*[b]
CYP2C19 poor metabolizer (approximately 2–15% of individuals)	An individual with 2 no function alleles	**2/*2* **2/*3* **3/*3*

CPIC: Clinical Pharmacogenetics Implementation Consortium
[a] CYP2C19 metabolizer status frequencies are based on average multi-ethnic frequencies. See the *CYP2C19* Frequency Tables for population-specific allele and phenotype frequencies (18).
[b] The predicted metabolizer phenotype for the**2/*17* genotype is a provisional classification. The available evidence indicates that the *CYP2C19*17* increased function allele is unable to completely compensate for the *CYP2C19*2* no function allele.
This CPIC table is adapted from (18).

It has been reported that approximately 2% of Caucasians, 4% of African Americans, and 14% of Chinese are CYP2C19 poor metabolizers; and up to 45% of individuals are CYP2C19 intermediate metabolizers (19). Other studies have found poor metabolizer phenotypes to range between 10.8–16.4% in Asian populations, 3% in African descendants, and 1.6% in Middle-Eastern populations (20, 21). Pacific Islanders have been reported to have higher frequencies of poor metabolizers—11.8% (21). The frequency of intermediate metabolizers is similarly distributed, higher in East and South Asian and Pacific Islander, lower in African or Middle-Eastern populations (20).

The 2018 FDA-approved drug label for omeprazole states that approximately 15–20% of Asians are CYP2C19 poor metabolizers, compared with 3% of Caucasians. And the label states that studies have shown that Asians have an approximately four-fold higher exposure to omeprazole than Caucasians.

The most common no function allele is *CYP2C19*2*, which contains a c.681G>A variant in exon 5 that results in an aberrant splice site. This leads to the production of a truncated and non-functioning protein. The *CYP2C19*2* allele frequencies are ~15% in Caucasians of European descent and Africans, and ~27–36% in Asians (20, 22).

*CYP2C19*3* is another commonly identified no function variant, which contains a c.636G>A variant in exon 4 that causes a premature stop codon. The *CYP2C19*3* allele frequencies are ~2–7% in Asian populations (22), but rare in other racial groups. Other no function variants occur in less than 1% of the general population and include *CYP2C19*4-*8* (23, 24).

The *CYP2C19*17* allele, which results in rapid and ultrarapid metabolizers, has frequencies of only 1.3–4% among Asian populations compared with approximately 20–33.7% of African,-European and Near-Eastern populations (20, 21).

Linking Gene Variation with Treatment Response

In adults, it has been established that genetic variation in *CYP2C19* influences PPI clearance and exposure, which are heavily metabolized by CYP2C19. Recent CPIC guidelines support increasing treatment failures in rapid and ultrarapid metabolizers and emerging adverse events in intermediate and poor metabolizers, particularly for chronic use (4). However, DPWG recommendations based on an independent review of the literature does not find compelling evidence for an increased risk to intermediate or poor metabolizers (2). Multiple reviews have recently been published describing the risks and potential adverse effects for long-term PPI use, supporting genotype-guided dosage and limited duration of PPI administration (25, 26, 27).

In pediatric studies, there are less data, yet some trends are emerging with decreased omeprazole efficacy (more acidic gastric pH) in CYP2C19 ultrarapid metabolizers (8, 28, 29, 30) and less adverse events with genotype-guided dosing. Pediatric individuals with increased function **17* alleles were more likely to experience GERD treatment failure with PPIs, requiring surgical intervention (31). One study observed a lower frequency of PPI-associated infection in pediatric rapid and ultrarapid metabolizers compared with normal metabolizers (32). Additional pediatric studies are needed.

Response of CYP2C19 Poor Metabolizers

Individuals with reduced CYP2C19 enzyme activity may have up to 2-fold higher plasma concentration of omeprazole with standard doses compared with individuals with normal enzyme function. Studies report that poor metabolizers have less acidic gastric pH than normal metabolizers, indicating higher activity (33, 34).

Some studies support a model whereby reduced or absent CYP2C19 enzyme activity has a positive effect on clinical outcomes and because PPIs are generally regarded as safe drugs, especially in the short-term (less than 6 months), this can have a beneficial effect without an increased risk of omeprazole toxicity (35, 36, 37, 38). However, emerging evidence links long-term PPI use with a higher risk of adverse events including bone fracture, GI infections—such as *Clostridium difficile*—hypomagnesemia, fundic gland polyps, interstitial nephritis, and vitamin B-12 deficiency (1, 26, 27).

One study reported that when using omeprazole as part of the treatment to eradicate *H. pylori*, success was achieved in all individuals who had little or no CYP2C19 activity, but in only 29% of individuals who had "normal" CYP2C19 activity. Similar results were found in another study that evaluated lansoprazole in the treatment of GERD: the response rate was 85% for individuals with little or no CYP2C19 activity, compared with 16% for individuals with normal CYP2C19 activity (39, 40, 41).

The emerging risk profile for PPI medications is of particular concern for CYP2C19 poor and intermediate metabolizers. Therefore, recent CPIC guidelines recommend a 50% reduction in daily dose of omeprazole for chronic therapy among poor and intermediate metabolizers (4). The DPWG guidelines do not recommend the reduced dose for these individuals (2). This discordance between CPIC and DPWG may stem from the recent emergence of data showing increased adverse effects with long-term PPI use.

Response of CYP2C19 Rapid and Ultrarapid Metabolizers

Individuals with increased CYP2C19 enzyme activity may experience subtherapeutic exposure to standard doses of omeprazole, compared with individuals with normal enzyme function (42). Several studies have reported an association between CYP2C19 ultrarapid metabolizers and incomplete acid suppression ("PPI resistance") and a decreased rate of eradication of *H. pylori* (37, 43, 44, 45). Based on the concerns of *CYP2C19* influenced treatment failure, recent CPIC guidelines recommend an increase in daily PPI dose by 100% in ultrarapid metabolizers and 50–100% in rapid metabolizers (4). The DPWG guidelines recommend that up to a 3-fold increase in dosage can be utilized for ultrarapid metabolizers for *H. pylori* eradication (2), this recommendation is based on review of pharmacokinetics reports for rapid and ultrarapid metabolizers. For more information on DPWG recommendations and justifications, please see (3).

Genotype-guided therapy for PPI administration has been shown to have higher success rates than empirical or standard dosing. Rapid and ultrarapid metabolizers with genotype-guided dosing showed a higher rate of efficacy in *H. pylori* eradication following triple therapy than standard dosing (46). Combined testing for bacterial drug-resistance and *CYP2C19* genotype also shows promise for improving therapeutic efficacy in the pediatric population (47).

The *CYP2C19* Gene Interactions with Medications Used for Additional Indications

Genetic variation in the *CYP2C19* gene influences the metabolism of other medications used for the treatment of several conditions such as:

- Acute coronary syndrome –– individuals who are CYP2C19 poor metabolizers and undergoing percutaneous coronary intervention have an increased risk of cardiovascular events if they are treated with the antiplatelet drug clopidogrel (a pro-drug that is activated by CYP2C19-mediated metabolism).
- Depression –– CYP2C19 influences the metabolism of tricyclic antidepressants (amitriptyline, imipramine); SSRIs (citalopram) and other serotonin receptor agonists (flibanserin). Individuals who are CYP2C19 poor metabolizers may have an increased risk of side effects, whereas CYP2C19 ultrarapid metabolizers may have an increased risk of treatment failure.
- Epilepsy — Brivaracetam, lacosamide, and clobazam are antiseizure drugs that are metabolized by CYP2C19, and poor metabolizers are at an increased risk of adverse events due to higher drug plasma concentrations. Diazepam is another drug with indications for seizure management that is metabolized by CYP2C19.
- Muscle pain—Carisoprodol is a muscle relaxant that is metabolized by CYP2C19, and poor metabolizers are at an increased risk of adverse events due to higher plasma concentration of carisoprodol, accompanied by lower active metabolite concentrations.
- Anti-fungal treatment—Voriconazole is a broad spectrum anti-fungal agent that is metabolized by CYP2C19 and both ultrarapid and poor metabolizers may require alternative medications.

Additional information on gene-drug interactions for *CYP2C19* are available from PharmGKB, CPIC and the FDA (search for "CYP2C19").

Genetic Testing

Clinical genotyping tests are available for several *CYP2C19* alleles. The NIH Genetic Testing Registry (GTR) provides examples of the genetic tests that are available for the omeprazole response and the *CYP2C19* gene.

Individual results are typically reported as a diplotype, such as *CYP2C19 *1/*1*, and may also include an interpretation with the predicted metabolizer phenotype (ultrarapid, rapid, normal, intermediate, or poor). Table 3 summarizes common CYP2C19 phenotypes.

In 2018, the Association for Molecular Pathology published recommendations for *CYP2C19* genotyping allele selection. The recommendations determined varying tiers of alleles, based on the strength of evidence supporting drug-response, minor allele frequencies and availability of reference materials. The Association's tier 1 group represent the core alleles recommended for genotyping panels: **2, *3,* and **17* (48). These guidelines provide information for laboratories performing *CYP2C19* genotype testing and are a useful complement to CPIC prescribing recommendations.

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

[1] The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug. Certain terms, genes and genetic variants may be corrected in accordance to nomenclature standards, where necessary. We have given the full name of abbreviations, shown in square brackets, where necessary.

2020 Statement from the US Food and Drug Administration (FDA)

Asian Population

In studies of healthy subjects, Asians had approximately a four-fold higher exposure than Caucasians. Dosage reduction of Omeprazole delayed-release capsules to 10 mg once daily is recommended for Asian patients for maintenance of healing of erosive esophagitis.

[…]

Pharmacogenomics

CYP2C19, a polymorphic enzyme, is involved in the metabolism of omeprazole. The *CYP2C19*1* allele is fully functional while the *CYP2C19*2* and **3* alleles are nonfunctional. There are other alleles associated with no or reduced enzymatic function. Patients carrying two fully functional alleles are normal metabolizers and those carrying two loss-of-function alleles are poor metabolizers. In normal metabolizers, omeprazole is primarily metabolized by CYP2C19. The systemic exposure to omeprazole varies with a patient's metabolism status: poor metabolizers > intermediate metabolizers > normal metabolizers. Approximately 3% of Caucasians and 15 to 20% of Asians are CYP2C19 poor metabolizers.

In a pharmacokinetic study of single 20 mg omeprazole dose, the AUC of omeprazole in Asian subjects was approximately four-fold of that in Caucasians.

[…]

Interaction with Clopidogrel

Avoid concomitant use of Omeprazole delayed-release capsules with clopidogrel. Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is entirely due to an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by use with concomitant medications, such as omeprazole, that inhibit CYP2C19 activity. Concomitant use of clopidogrel with 80 mg omeprazole reduces the pharmacological activity of clopidogrel, even when administered 12 hours apart. When using Omeprazole delayed-release capsules, consider alternative anti-platelet therapy.

[…]

Clinically relevant interactions affecting Omeprazole delayed-release capsules when co-administered with other drugs

CYP2C19 or CYP3A4 Inducers	
Clinical Impact:	Decreased exposure of omeprazole when used concomitantly with strong inducers
Intervention:	St. John's Wort, rifampin: Avoid concomitant use with Omeprazole delayed-release capsules Ritonavir-containing products: see prescribing information for specific drugs.
CYP2C19 or CYP3A4 Inhibitors	
Clinical Impact:	Increased exposure of omeprazole
Intervention:	Voriconazole: Dose adjustment of Omeprazole delayed-release capsules are not normally required. However, in patients with Zollinger-Ellison syndrome, who may require higher doses, dose adjustment may be considered. See prescribing information for voriconazole.

Please review the complete therapeutic recommendations located here: (1).

2020 Summary of recommendations from the Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for *CYP2C19* and Proton Pump Inhibitor Dosing

Therapeutic Recommendations

Table 2 summarizes therapeutic recommendations for PPI prescribing in adults and pediatric patients based on CYP2C19 phenotype, specifically for the first-generation PPIs (omeprazole, lansoprazole, pantoprazole) and dexlansoprazole. These recommendations apply to both oral and intravenous PPI use. While CYP2C19 [normal metabolizers] NMs are expected to have normal PPI metabolism and clearance, a large body of literature from studies in Asian populations reported an association between CYP2C19 NMs and decreased therapeutic effectiveness with these PPIs (e.g., failure to eradicate *H. pylori* infection and lower healing rates of erosive esophagitis) compared to CYP2C19 [intermediate metabolizers] IMs and [poor metabolizers] PMs (Tables S1-S4). Therefore, for CYP2C19 NMs, 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.

[…]

It has been suggested that continued inhibition of acid secretion in individuals taking PPIs chronically who are genotyped as CYP2C19 IMs or PMs may have a higher risk of PPI-related adverse events compared to NM, [rapid metabolizer] RM, or [ultrarapid metabolizer] UM phenotypes (1). 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 (24). Therefore, for CYP2C19 IMs and PMs, 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. If a dose reduction is made, monitoring for continued efficacy is recommended. Additional studies that investigate the relationship between *CYP2C19* genotype and incidence of PPI-related adverse events are needed.

The RM and UM phenotypes are driven by the presence of the increased function *CYP2C19*17* allele. Due to the relatively recent discovery of this variant (11) 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 RMs and UMs. … Therefore, it is recommended to increase the starting daily dose by 100% in CYP2C19 UMs. For RMs, standard dosing should be initiated, but a 50-100% dose increase could be considered for the treatment of H. pylori infection and erosive esophagitis to maximize the likelihood of therapeutic plasma concentrations and therapeutic effect. These patients should be monitored for efficacy.

[…]

Pediatrics

The *CYP2C19*-guided PPI recommendations presented in Table 2 also apply to pediatric patients.

Please review the complete therapeutic recommendations located here: (4).

2018 Summary of recommendations from the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP)

CYP2C19 Poor Metabolizer

NO action is required for this gene-drug interaction.

The higher plasma concentration of omeprazole results in an increase in the therapeutic effectiveness, without an increase in the side effects.

CYP2C19 Intermediate Metabolizer

NO action is required for this gene-drug interaction.

The higher plasma concentration of omeprazole results in an increase in the therapeutic effectiveness, without an increase in the side effects.

CYP2C19 Ultrarapid Metabolizer

The genetic variation may lead to a reduced omeprazole plasma concentration and therefore reduced effectiveness.

Recommendation:

For *Helicobacter pylori* ERADICATION THERAPY:

- use a 3-fold higher dose
- advise the patient to report persisting symptoms of dyspepsia

OTHER INDICATIONS:

- be alert to reduced effectiveness
- if necessary, use a 3-fold higher dose
- advise the patient to contact their doctor if symptoms of dyspepsia persist

Background information

Mechanism:

Omeprazole is primarily converted by CYP2C19 to inactive metabolites.

Omeprazole inhibits CYP2C19 and therefore its own metabolism. This leads to non-linear pharmacokinetics. The AUC response to dose increases is greater than linear in normal metabolizer patients at doses exceeding 40 mg.

For more information about the UM phenotype: see the general background information about CYP2C19 on the KNMP Knowledge Bank or on www.knmp.nl (search for CYP2C19).

Please review the complete therapeutic recommendations that are located here: (2, 3).

Nomenclature for Selected *CYP2C19* Alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2C19*2*	681G>A Pro227Pro	NM_000769.4:c.681G>A	NP_000760.1:p.Pro227=	rs4244285
*CYP2C19*3*	636G>A Trp212Ter	NM_000769.4:c.636G>A	NP_000760.1:p.Trp212Ter	rs4986893
*CYP2C19*4*	1A>G Met1Val	NM_000769.4:c.1A>G	NP_000760.1:p.Met1Val	rs28399504
*CYP2C19*5*	90033C>T Arg433Trp	NM_000769.4:c.1297C>T	NP_000760.1:p.Arg433Trp	rs56337013
*CYP2C19*6*	12748G>A Arg132Gln	NM_000769.4:c.395G>A	NP_000760.1:p.Arg132Gln	rs72552267
*CYP2C19*7*	19294T>A	NM_000769.4:c.819+2T>A	(Splice donor variant)	rs72558186
*CYP2C19*8*	12711T>C Trp120Arg	NM_000769.4:c.358T>C	NP_000760.1:p.Trp120Arg	rs41291556
*CYP2C19*9*	12784G>A Arg144His	NM_000769.4:c.431G>A	NP_000760.1:p.Arg144His	rs17884712
*CYP2C19*17*	-806C>T	NM_000769.4:c.-806C>T	Not applicable - variant occurs in a non-coding region	rs12248560

Note: when no variants are detected the genotype is designated as *CYP2C19*1* and is considered the normal "wild-type" allele.
Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting (49).
Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS).
Nomenclature for Cytochrome P450 enzymes is available from the Pharmacogene Variation (PharmVar) Consortium.

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Previous Versions

To view the version of this Summary from 8 March 2016, please click here.

To view the version of this Summary from 18 March 2013, please click here.

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