Esomeprazole Therapy and *CYP2C19* Genotype

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Esomeprazole blocks the secretion of gastric acid and belongs to the drug class of proton pump inhibitors. It is used to treat gastroesophageal reflux disease (GERD), to eradicate *H. pylori* infection, and to reduce the risk of gastric ulcers associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs).

Esomeprazole is metabolized by the enzymes CYP3A4 and CYP2C19. In individuals who have reduced or absent CYP2C19 enzyme activity, the recommended doses of esomeprazole may lead to higher exposure to the drug and increased clinical efficacy. In contrast, individuals with increased CYP2C19 activity ("ultrarapid metabolizers") may be exposed to lower levels of esomeprazole.

Currently, the FDA does not provide recommendations about the use of *CYP2C19* genetic testing for esomeprazole treatment ([1]). However, the Dutch Pharmacogenetics Working Group recommends dose alterations based on *CYP2C19* genotype. For the eradication of *H. pylori* in ultrarapid metabolizers, they recommend a 50–100% increase of esomeprazole dose. The same dose increase should also be considered for the treatment of other conditions (see Table 1) ([2, 3]).

Table 1.

CYP2C19 phenotypes and the therapeutic recommendations for esomeprazole therapy

Phenotype	Phenotype details	Examples of diplotypes	Therapeutic recommendations for esomeprazole
Ultrarapid metabolizer	Normal or increased CYP2C19 activity	**17/*17*	Be extra alert to insufficient response. For the eradication of *H. pylori* , increase dose by 50–100%. For other conditions, consider dose increase by 50–100%.
Extensive metabolizer	Normal CYP2C19 activity	**1/*1*	Dose recommended by drug label
Intermediate metabolizer	Decreased CYP2C19 activity	**1/*2* **1/*3* **2/*17* **3/*17*	Dose recommended by drug label
Poor metabolizer	Markedly reduced or absent CYP2C19 activity	**2/*2* **2/*3* **3/*3*	Dose recommended by drug label

Good quality evidence supports the dose recommendations for poor and intermediate metabolizers; data are lacking for ultrarapid metabolizers.

Table is adapted from Swen J.J., Nijenhuis M., de Boer A., Grandia L. et al. Pharmacogenetics: from bench to byte - an update of guidelines. Clinical pharmacology and therapeutics. 2011;89([5]):662–73 ([3]).

Drug: Esomeprazole

Esomeprazole, like all proton pump inhibitors, blocks gastric acid secretion in a dose-dependent manner. It acts by inhibiting the H^+-K^+-ATPase ("proton pumps") in gastric parietal cells ([4]).

Esomeprazole is metabolized in the liver by the cytochrome P450 system. Most of the drug is metabolized by the CYP3A4 enzyme, with the CYP2C19 enzyme having a lesser role ([5]).

For many proton pump inhibitors, the activity of CYP2C19 influences the level of drug exposure, drug response (higher pH), and clinical outcome (eradication of *H. pylori* , healing rates of peptic ulcers, and GERD) ([6]). Individuals with reduced CYP2C19 enzyme activity may experience twice the drug exposure compared to individuals with normal enzyme function ([1]), which can have a positive clinical effect ([7, 8]). Patients with increased CYP2C19 activity may require an increased dose of esomeprazole to compensate for the increased rate of drug metabolism.

However, the efficacy of esomeprazole appears to be less effected by *CYP2C19* genotype, at least for the treatment of GERD. This is because of the shift towards CYP3A4-mediated metabolism and elimination of the drug ([4]).

Gene: *CYP2C19*

The cytochrome P450 superfamily (CYP) is a large and diverse group of enzymes, which together form the major system for metabolizing drugs. The CYP genes are often polymorphic and can result in either reduced or absent drug metabolism, or conversely, increased drug metabolism.

CYP2C19 is involved in the metabolism of many drugs, and the *CYP2C19* gene is highly polymorphic with more than 25 currently known variants. *CYP2C19*1* is the wild-type allele and is associated with normal enzyme activity. Individuals who are homozygous for the **1* allele are known as "extensive metabolizers"([9]).

The most common loss-of-function variant is *CYP2C19*2* (c.681G>A), which has allele frequencies of ~15% in Caucasians and Africans, and 29–35% in Asians ([5]). It is inherited as an autosomal co-dominant trait ([10]). "Intermediate metabolizers" carry one copy of an allele that encodes reduced or absent function (e.g., **1/*2*), whereas "poor metabolizers" are homozygous for two loss-of-function alleles (e.g., **2/*2*).

Around 3% of Caucasians and 15–20% of Asians are poor metabolizers. At steady state, the ratio of AUC (area under the plasma concentration-time curve) in poor metabolizers to AUC in the rest of the population (extensive metabolizers) is approximately 2 ([1]).

In contrast to non-functional alleles, the *CYP2C19*17* allele (c.-806C>T) is associated with increased enzyme activity. Allele frequencies range from 3 to 21% in different populations ([10]). Individuals who are homozygous for the **17* allele are known as "ultrarapid metabolizers", and it is this patient group who may benefit from an increased dose of esomeprazole. However, not all studies have identified a significant effect of *CYP2C19*17* on the metabolism of proton pump inhibitors and treatment outcomes ([7, 11, 12]).

Genetic Testing

Genetic testing is available for several *CYP2C19* variant alleles, including the **17* allele ([7]). Currently, the FDA does not provide recommendations about the use of *CYP2C19* genetic testing for esomeprazole treatment ([1]).

Therapeutic Recommendations based on Genotype

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

Summary of recommendations from the Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy (KNMP): For individuals who are ultrarapid metabolizers, physicians should be vigilant to an insufficient response to esomeprazole therapy. For the eradication of *H. pylori* , the dose of esomeprazole should be increased by 50–100%.

Please review the complete therapeutic recommendations that are located here: ([3]).

Nomenclature

Common allele name	Variant	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2C19*2*	681G>A (Pro227Pro)	NM_000769.1:c.681G>A	NP_000760.1:p.Pro227=	rs4244285
*CYP2C19*17*	-806C>T	NM_000769.1:c.-806C>T	Not applicable—variant occurs in a (non-coding) promoter region	rs12248560

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS): http://www.hgvs.org/content/guidelines

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Tests in GTR by Condition

Esomeprazole response

Tests in GTR by Gene

CYP2C19 gene

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