



Esomeprazole Therapy and CYP2C19 Genotype

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Introduction

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) and to reduce the risk of gastric ulcers associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs). Esomeprazole is also used in the treatment of hypersecretory conditions, such as Zollinger-Ellison syndrome, and is used in combination with antibiotics to eradicate *Helicobacter pylori* (*H. pylori*) infection (1).

Esomeprazole is metabolized primarily by the CYP2C19 enzyme. Approximately 3% of Caucasians and 15 to 20% of Asians have reduced or absent CYP2C19 enzyme activity (“poor metabolizers”). In these individuals, standard doses of esomeprazole leads to higher exposure of the drug (2). In contrast, individuals with increased CYP2C19 activity (“ultrarapid metabolizers”) may be exposed to lower levels of esomeprazole and have an insufficient response to treatment.

The FDA-approved drug label for esomeprazole states that poor metabolizers are exposed to approximately twice the level of drug compared to the rest of the population (“extensive metabolizers”), but the label does not require dose changes for poor metabolizers (1). However, the Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy (KNMP) has published dose alterations based on CYP2C19 genotype. For CYP2C19 poor metabolizers, they do not recommend altering the dose; however for ultrarapid metabolizers, they recommend being extra alert to an insufficient response to treatment. For the eradication of *H. pylori* in ultrarapid metabolizers, KNMP recommends increasing the dose of omeprazole by 50–100%, and to consider the same dose increase for other conditions (see Table 1) (3, 4).

Table 1. CYP2C19 phenotypes and the therapeutic recommendations for esomeprazole therapy, adapted from the Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy (KNMP).

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 <i>H. pylori</i> , increase dose by 50–100%. For other conditions, consider dose increase by 50–100%.
Extensive metabolizer	Normal CYP2C19 activity	*1/*1	No recommendations

Table 1. continued from previous page.

Phenotype	Phenotype details	Examples of diplotypes	Therapeutic recommendations for esomeprazole
Intermediate metabolizer	Decreased CYP2C19 activity	*1/*2 *1/*3 *2/*17 *3/*17	No recommendations
Poor metabolizer	Markedly reduced or absent CYP2C19 activity	*2/*2 *2/*3 *3/*3	No recommendations

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 (4).

Drug class: Proton Pump Inhibitors

Proton pump inhibitors (PPIs) are inhibitors of gastric acid secretion that are used in the treatment of stomach-acid related disorders. PPIs are also used to prevent and treat ulcers associated with nonsteroidal anti-inflammatory drugs (NSAIDs), and can be used in combination with antibiotics to eradicate *H. pylori* infection.

Six PPIs are currently FDA-approved for clinical use: esomeprazole, dexlansoprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole. All PPIs are similarly potent at inhibiting gastric acid secretion and are thought to be similarly efficacious (5, 6).

PPIs are metabolized and inactivated by a number of CYP enzymes, including CYP2C19, which has a principal role in the metabolism of omeprazole. The increased function *CYP2C19*17* variant allele may enhance PPI clearance (7) resulting in less active PPI available to inhibit gastric acid secretion. In contrast, the *CYP2C19*2* loss-of-function allele is associated with decreased PPI clearance, resulting in more active PPI available and enhanced treatment. For several PPIs, including omeprazole and lansoprazole, higher drug levels in patients with low or absent CYP2C19 activity have been associated with increased drug efficacy and improved treatment outcomes (2, 8).

Drug: Esomeprazole

Esomeprazole is used in the treatment of GERD in both adults and children. In adults, esomeprazole is also used to reduce the risk of developing a gastric ulcer associated with NSAID use, and in the treatment of pathological hypersecretory conditions such as Zollinger-Ellison syndrome (1).

The human stomach contains approximately one billion parietal cells that secrete hydrochloric acid (HCl) into the gastric lumen. Gastric acid aids digestion by hydrolyzing dietary protein and facilitating the absorption of calcium, iron, and vitamin B. Gastric acid also helps maintain a sterile environment by suppressing the growth of bacteria (9).

Hydrogen ions (H⁺) are actively secreted in to 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 surface of gastric parietal cells, the proton pump controls the last step in acid secretion, and by targeting this step, esomeprazole and the other PPIs are able to potently inhibit gastric acid secretion.

Esomeprazole is metabolized in the liver by the cytochrome P450 system to inactive metabolites. CYP2C19 metabolizes esomeprazole to hydroxy and desmethyl metabolites, and the remaining drug is metabolized by CYP3A4 to sulphone metabolites (1).

Individuals with reduced *CYP2C19* enzyme activity may experience twice the exposure to esomeprazole compared to individuals with normal enzyme function. For other PPIs, such as omeprazole and lansoprazole, increased drug levels are associated with improved clinical outcomes (10, 11). For example, one study reported that when using omeprazole as part of the treatment to eradicate *H. pylori*, success was achieved in all patients who had little or no *CYP2C19* activity, but in only 29% of patients who had “normal” *CYP2C19* activity. Similar results were found in another study that evaluated lansoprazole in the treatment of GERD: the cure rate was 85% for patients with little or no *CYP2C19* activity, compared to 16% for patients with normal *CYP2C19* activity (12-14).

However, the efficacy of esomeprazole appears to be less influenced by *CYP2C19* genotype, at least for the treatment of GERD (15-17). This may be because of the shift towards *CYP3A4*-mediated metabolism and elimination of the drug (9).

The FDA-approved drug label for esomeprazole does not comment on dose adjustments based on *CYP2C19* status. However, guidelines from KNMP recommend that patients with increased *CYP2C19* activity (“ultrarapid metabolizers”) should receive an increased dose of esomeprazole for the eradication of *H. pylori*, and that an increased dose should be considered for other indications (Table 1).

The long-term use of PPIs has been associated with several adverse effects. Daily treatment with any PPI for longer than three years may lead to malabsorption of vitamin B12, caused by hypochlorhydria. Because prolonged hypochlorhydria also increases the risk of *Clostridium difficile* infection, and may increase the risk for osteoporosis-related fractures, the FDA recommends that patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated (1).

Gene: *CYP2C19*

The cytochrome P450 superfamily (CYP) is a large and diverse group of 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, such as antidepressants, benzodiazepines, and some of the PPIs, including esomeprazole.

CYP2C19 is highly polymorphic, as 35 variant star (*) alleles are currently catalogued at the Human Cytochrome P450 (CYP) Allele Nomenclature Database (<http://www.cypalleles.ki.se/cyp2c19.htm>). The *CYP2C19**1 wild-type allele is associated with normal enzyme activity and the “extensive metabolizer” phenotype (18).

The most common loss-of-function variant 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 and Africans, and ~29–35% in Asians (19). “Intermediate metabolizers” carry one copy of an allele that encodes reduced or absent function (e.g. *1/*2), whereas “poor metabolizers” are homozygous or compound heterozygous for two loss-of-function alleles (e.g., *2/*2, *2/*3).

Another commonly tested loss-of-function variant is *CYP2C19**3, which contains a c.636G>A variant in exon 4 that causes a premature stop codon. The *CYP2C19**3 allele frequencies are ~2–9% in Asian populations, but rare in other racial groups. Other loss-of-function variants occur in less than 1% of the general population, and include *CYP2C19**4- *8 (19, 20).

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% across different populations (21). 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 omeprazole. However, not all studies have identified a significant effect of *CYP2C19**17 on the metabolism of PPIs and treatment outcomes (14, 22, 23).

Genetic Testing

Currently, the FDA does not provide recommendations about the use of *CYP2C19* genetic testing for esomeprazole treatment (1).

Clinical genotyping tests are available for several *CYP2C19* alleles, and a list of some test providers is available at the Genetic Testing Registry (GTR) of the National Institutes of Health: [http://www.ncbi.nlm.nih.gov/gtr/tests/?term=1557\[geneid\]](http://www.ncbi.nlm.nih.gov/gtr/tests/?term=1557[geneid]).

Usually a patient's result is reported as a diplotype, such as *CYP2C19* *1/*1, and may also include an interpretation of the patient's predicted metabolizer phenotype (ultrarapid, extensive, intermediate, or poor).

Table 1 summarizes common *CYP2C19* phenotypes with recommendations developed by the Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy (KNMP).

Therapeutic Recommendations based on Genotype

This section contains excerpted¹ information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2015 Statement from the US Food and Drug Administration (FDA): Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system. The metabolites of esomeprazole lack antisecretory activity. The major part of esomeprazole's metabolism is dependent upon the *CYP2C19* isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on *CYP3A4* which forms the sulphone metabolite. *CYP2C19* isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15 to 20% of Asians lack *CYP 2C19* and are termed Poor Metabolizers. At steady state, the ratio of AUC in Poor Metabolizers to AUC in the rest of the population (Extensive Metabolizers) is approximately 2.

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

2011 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: (4).

Nomenclature

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
<i>CYP2C19</i> *2	681G>A Pro227Pro	NM_000769.1:c.681G>A	NP_000760.1:p.Pro227=	rs4244285
<i>CYP2C19</i> *3	636G>A Trp212Ter	NM_000769.1:c.636G>A	NP_000760.1:p.Trp212Ter	rs4986893
<i>CYP2C19</i> *17	-806C>T	NM_000769.2:c.-806C>T	Not applicable—variant occurs in a non-coding region	rs12248560

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 labelled all formulations containing the generic drug.

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

Nomenclature for Cytochrome P450 enzymes is available from the Human Cytochrome P450 (CYP) Allele Nomenclature Database: <http://www.cypalleles.ki.se/>

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Version History

To view an earlier version of this summary (update: 18 March 2013), please click [here](#).

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