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Esomeprazole Therapy and *CYP2C19* Genotype

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Introduction

Esomeprazole (brand name Nexium) is a proton pump inhibitor (PPI) used to treat gastroesophageal reflux disease (GERD) and to reduce the risk of gastric ulcers associated with nonsteroidal anti-inflammatory drug NSAID use. Esomeprazole is also used in the treatment of hypersecretory conditions, such as Zollinger-Ellison syndrome, and in combination with antibiotics to eradicate *Helicobacter pylori (H. pylori)* infection.

Esomeprazole reduces the acidity (raises the pH) in the stomach by inhibiting the secretion of gastric acid. The level of esomeprazole an individual is exposed to is influenced by several factors, such as the dose used and how quickly the drug is metabolized and inactivated.

Esomeprazole is primarily metabolized by the CYP2C19 enzyme. Individuals with increased CYP2C19 enzyme activity ("CYP2C19 ultrarapid metabolizers") may have an insufficient response to standard doses of esomeprazole, because the drug is inactivated at a faster rate. In contrast, individuals who have reduced or absent CYP2C19 enzyme activity (i.e., CYP2C19 intermediate and poor metabolizers) have a greater exposure to esomeprazole.

The 2018 FDA-approved drug label for esomeprazole states that 3% of Caucasians, and 15–20% of Asians are CYP2C19 poor metabolizers, and that poor metabolizers have approximately twice the level of exposure to esomeprazole, compared with CYP2C19 normal metabolizers. However, the drug label does not include dosing recommendations for CYP2C19 poor metabolizers (1).

Esomeprazole recommendations have been published by the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP), which indicates that no change in dosing is recommended for CYP2C19 poor, intermediate, or ultrarapid metabolizers. The DPWG states that although genetic variation in *CYP2C19* influences the plasma concentration of esomeprazole, there is insufficient evidence to support an effect on treatment outcomes or side effects (2).

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Table 1. The FDA (2018) Drug Label for Esomeprazole: *CYP2C19*

Phenotype	Esomeprazole
CYP2C19 poor metabolizer	The CYP2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15–20% of Asians lack CYP2C19 and are termed poor metabolizers. At steady state, the ratio of AUC in poor metabolizers to AUC in the rest of the population (normal metabolizers) is approximately 2.

AUC: Area Under the plasma drug concentration-time Curve. AUC reflects the body's exposure to the drug being administered.
Note: "normal metabolizers" were previously termed "extensive metabolizers".
Please see Therapeutic Recommendations based on Genotype for more information from FDA. This FDA table is adapted from (1).

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

Phenotype	Action	Pharmacist text
CYP2C19 poor metabolizer	No action is required for this gene-drug interaction.	Although the genetic variation leads to a higher plasma concentration of esomeprazole, there is insufficient evidence to support an effect on the therapeutic effectiveness and side effects.
CYP2C19 intermediate metabolizer	No action is required for this gene-drug interaction.	
CYP2C19 ultrarapid metabolizer	No action is required for this gene-drug interaction.	Although the genetic variation may lead to faster inactivation of esomeprazole, there is insufficient evidence to support an effect on the therapeutic effectiveness and side effects.

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

Drug class: Proton Pump Inhibitors

Proton pump inhibitors block the secretion of gastric acid. They are among the most commonly prescribed drugs in the United States and globally, and some PPI formulations are available without a prescription.

Proton pump inhibitors can be used to treat a number of conditions in adults:

- Active duodenal ulcers
- Active gastric (peptic) ulcers
- *Helicobacter pylori* infection eradication (in combination with antibiotics, to reduce the risk of duodenal ulcer recurrence)
- Hypersecretory conditions (e.g., Zollinger-Ellison syndrome)

Proton pump inhibitors are also used in infants, children, and adults to treat:

- Symptomatic GERD
- Erosive esophagitis (EE) due to acid-mediated GERD
- Maintenance of healing of EE due to acid-mediated GERD

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 B. Gastric acid also helps maintain a sterile environment by suppressing the growth of bacteria (3).

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. Proton pump inhibitors potently suppress gastric acid secretion by covalently binding to and irreversibly inactivating this proton pump.

Six PPIs are currently FDA-approved for clinical use: 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 (4, 5).

There are a few differences between the 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 indicated from one year of age, omeprazole and dexlansoprazole from 2 years of age, and rabeprazole from age 12) (6).

All 6 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, and thus, the concurrent administration of omeprazole with clopidogrel must balance overall risks and benefits, considering both cardiovascular and gastrointestinal complications (7-11).

Genetic variation in the *CYP2C19* gene influences the clearance of PPIs, which may in turn influence treatment outcomes. Second-generation PPIs are being developed that are not primarily metabolized by CYP2C19, and therefore less likely to be influenced by *CYP2C19* genotype (12-14).

Drug: Esomeprazole

Esomeprazole is a PPI that is available via prescription medication or over-the-counter. It is closely related to omeprazole, which was the first PPI to be licensed in the United States. Esomeprazole is the S-isomer of omeprazole (mirror image of the same chemical structure) whereas omeprazole is a racemic mixture (50:50 mix) of R- and S-isomers.

In adults, esomeprazole is used to reduce the risk of NSAID-associated gastric ulcers and to reduce the risk of recurrence of duodenal ulcers by eradicating *H. pylori* infection. Esomeprazole is also used to treat pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

Esomeprazole is used to treat GERD and to support healing of EE in adults, children, and infants from one month of age.

Esomeprazole is metabolized and inactivated in the liver by the cytochrome P450 system. CYP2C19 is the principal enzyme involved, although other enzymes such as CYP3A4 also contribute to a lesser degree.

The long term use of PPIs has been associated with several adverse effects. Daily treatment with any PPI for longer than 3 years may lead to malabsorption of vitamin B12, caused by hypochlorhydria. Given that prolonged hypochlorhydria also increases the risk of *Clostridium difficile* infection and may increase the risk for osteoporosis-related fractures, the FDA recommends that individuals should use the lowest dose and shortest duration of PPI therapy appropriate for the condition being treated (1).

Studies have not adequately assessed the safety of esomeprazole therapy during pregnancy. For omeprazole use during pregnancy, epidemiology studies failed to find an increased risk of major congenital malformations or other adverse pregnancy outcomes.

Studies have reported that genetic variations in the *CYP2C19* gene influence the plasma concentration of esomeprazole. However, there is insufficient evidence to support that *CYP2C19* genotype influences the efficacy or safety of esomeprazole therapy (15-21). For other PPIs, such as omeprazole, alterations in dose have been recommended by the FDA and the DPWG (1, 2, 16).

Incidental Findings

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

- 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 prodrug that is activated via CYP2C19 metabolism)
- Depression – *CYP2C19* influences the metabolism of tricyclic antidepressants e.g., amitriptyline, imipramine; and selective serotonin reuptake inhibitors (SSRIs) e.g., citalopram. Individuals who are CYP2C19 poor metabolizers may have an increased risk of side effects, whereas there may be an increased risk of treatment failure in ultrarapid metabolizers.

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 currently available for the esomeprazole response and the *CYP2C19* gene. In addition, variant *CYP2C19* alleles to be included in clinical genotyping assays have been recommended by the Association for Molecular Pathology (22).

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, normal, intermediate, or poor).

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.

2018 Statement from the US Food and Drug Administration (FDA)

Metabolism

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 CYP2C19 and are termed Poor Metabolizers. At steady state, the ratio of AUC in Poor Metabolizers to AUC in the rest of the population (Normal Metabolizers) is approximately 2.

[...]

Interaction with Clopidogrel

Avoid concomitant use of esomeprazole magnesium 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 esomeprazole, that inhibit

[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 with nomenclature standards, where necessary. We have given the full name of abbreviations, shown in square brackets, where necessary.

CYP2C19 activity. Concomitant use of clopidogrel with 40 mg esomeprazole reduces the pharmacological activity of clopidogrel. When using esomeprazole magnesium consider alternative anti-platelet therapy.

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

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 (PM)

No action is needed for this gene-drug interaction.

Although the genetic variation leads to a higher plasma concentration of esomeprazole, there is insufficient evidence to support an effect on the therapeutic effectiveness and side effects.

CYP2C19 Intermediate Metabolizer (IM)

No action is needed for this gene-drug interaction.

Although the genetic variation leads to a higher plasma concentration of esomeprazole, there is insufficient evidence to support an effect on the therapeutic effectiveness and side effects.

CYP2C19 Ultrarapid Metabolizer (UM)

No action is required for this gene-drug interaction.

Although the genetic variation may lead to faster inactivation of esomeprazole, there is insufficient evidence to support an effect on the therapeutic effectiveness and side effects.

Background information

For more information about the PM, IM, and UM phenotypes: see the general background information about *CYP2C19* on the KNMP Knowledge Bank or on www.knmp.nl (search for *CYP2C19*). Access requires KNMP membership.

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

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