



# Rabeprazole

Joseph Cusimano *et al.*

## Abstract

Rabeprazole is a [proton pump inhibitor](#) that suppresses [gastric acid](#) production in the stomach. Available under different brand name products as well as in a variety of combination products, rabeprazole has several medical uses concerning the management of problems of pathological gastric acid. Rabeprazole's adverse effects tend to be mild but can be serious, including deficiencies in essential nutrients, rare incidences of liver damage, and immune-mediated reactions. As a class effect, rabeprazole can increase the risk for [osteoporosis](#), serious infections (including *Clostridium difficile* infections), and kidney damage. Rabeprazole can theoretically contribute to numerous [drug interactions](#), mediated both through its metabolic properties and its direct effect on acid in the [stomach](#), though its potential for clinically meaningful drug interactions is low. Like other medications in the proton pump inhibitor class, rabeprazole's mechanism of action involves the irreversible inhibition of proton pumps in the stomach, which are responsible for gastric acid production. Rabeprazole has a number of chemical [metabolites](#), though it is primarily degraded by non-enzymatic metabolism and excreted in the urine. Genetic differences in a person's drug-metabolizing [enzymes](#) may theoretically affect individual responses to rabeprazole therapy, though the clinical significance of this interaction is unlikely in comparison to other proton pump inhibitors. The purpose of this review is to provide an up-to-date monograph on rabeprazole.

**Keywords:** (RS)-rabeprazole, proton-pump inhibitors, drugs for acid-related disorders

## Medical uses

Rabeprazole, like other [proton pump inhibitors](#) (PPIs) such as [omeprazole](#) and [lansoprazole](#), is used for the purpose of gastric acid suppression.<sup>[1]</sup> This effect is beneficial for the treatment and prevention of conditions in which gastric acid directly worsens symptoms, such as duodenal and gastric ulcers.<sup>[1]</sup> In the setting of [gastroesophageal reflux disease](#) (GERD), whose pathophysiology is characterized by prolonged exposure to gastric acid in the esophagus (often due to changes in stomach and/or esophagus anatomy, such as those induced by abdominal obesity),<sup>[2]</sup> acid suppression can provide symptomatic relief.<sup>[1]</sup> Acid suppression is also useful when gastric production of acid is increased, including rare conditions with excess gastric acid secretion (hypersecretory conditions) like [Zollinger-Ellison syndrome](#) (ZES), [multiple endocrine neoplasia type 1](#) (MEN-1), and systemic [mastocytosis](#).<sup>[1]</sup> In an [open-label](#), industry-sponsored, [non-controlled](#) study of high-dose rabeprazole for the treatment of ZES and idiopathic gastric acid hypersecretion (IGAH), including patients with MEN-1 and GERD, rabeprazole induced and

maintained suppression of basal acid output over a 24 month period.<sup>[3]</sup> Only one patient withdrew from the study due to an elevation in [creatinine phosphokinase](#) judged to be possibly due to rabeprazole, while rabeprazole was otherwise well-tolerated in this population.<sup>[3]</sup> There are no clinical trials to date that have studied the precise use of rabeprazole, or any PPI, for the treatment of acid-related complaints due to systemic mastocytosis, but acid suppressing medications such as PPIs and [H2 receptor antagonists](#) are routinely used to counter the histamine-mediated acid secretion found in this disorder.<sup>[4]</sup>

Rabeprazole has utility alongside antibiotic therapy for the treatment of the pathogen *Helicobacter pylori* (*H. pylori*), which otherwise thrives in acidic environments.<sup>[1]</sup> In the original studies that gave rise to its approval for the eradication of *H. pylori*, rabeprazole was studied in combination with amoxicillin and clarithromycin. This triple therapy was studied at the specific doses of rabeprazole 20mg twice daily, amoxicillin 1000mg twice daily, and clarithromycin 500mg twice daily for 7 days, which is a higher dose of rabeprazole than what is used for the treatment of simple GERD (20mg once daily). The higher dose is thought to provide more consistent elevation of pH in the stomach, leading to better eradication of *H. pylori*, congruent

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with the dosing strategies of other PPIs for this indication.<sup>[5]</sup> Notably, *H. pylori* eradication with antibiotics and rabeprazole was also shown to prevent development of second gastric cancer in a randomized trial in high-risk South Korean patients with early stomach cancer treated by endoscopy.<sup>[6]</sup>

Thus, rabeprazole is FDA approved for:

- treatment of symptomatic GERD in adolescents and adults,
- healing duodenal ulcers in adults,
- eradication of *Helicobacter pylori*, and
- pathologic hypersecretory conditions.<sup>[7]</sup>

### Available forms

The only available formulation of rabeprazole is in 20 mg, delayed-release tablets (see Figures 1 and 2).<sup>[7]</sup> Rabeprazole-based products, like other proton pump inhibitor products, have to be formulated in delayed-release tablets to protect the active medication from being degraded by the acid of the stomach before being absorbed.<sup>[8]</sup>



Figure 1 | Brand name rabeprazole tablets. Elbreapoly, public domain



Figure 2 | Bottle of rabeprazole 20 mg tablets. Elbreapoly, public domain

## Specific populations

### Pediatrics

Rabeprazole's only pediatric indication is for the treatment of symptomatic GERD in adolescents (12 years-old and up).<sup>[7]</sup>

### Pregnancy

The FDA originally labeled rabeprazole as a pregnancy category B drug (meaning that *in vivo* research failed to demonstrate a fetal hazard, though human studies are lacking),<sup>[9]</sup> but it was reclassified as a pregnancy category C drug (meaning that *in vivo* research has shown a fetal hazard, though the benefit of use may outweigh the risk) in 2014.<sup>[10][11]</sup> This was after the publishing of an *in vivo* study that detected changes in bone morphology in rats treated with esomeprazole.<sup>[12]</sup> In these rats, the following observations were noted:<sup>[12][13]</sup>

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- shortened femurs, decreased width and thickness of cortical bone, decreased thickness of the tibial growth plate, and minimal to mild bone marrow hypocellularity occurred at doses equal to or greater than 3.4 times the daily maximum recommended human dose (MRHD);
- decreased survival, decreased birth weight, and an increase in neurobehavioral delays occurred at doses equal to or greater than 16.8 times the daily MRHD;
- physeal dysplasia of the femur occurred at doses equal to or greater than 33.6 times the daily MRHD.

*In vivo* studies on rabbits with rabeprazole doses of up to 50mg/kg/day (about 13 times the normal human drug exposure of rabeprazole at 20mg) failed to show evidence of fetal harm.<sup>[12]</sup>

### Lactation

It is expected that rabeprazole will be secreted into human breast milk, though the clinical impact of this is still



unknown. Avoiding rabeprazole during [breastfeeding](#) confers the lowest possible risk.<sup>[1]</sup>

### Geriatrics

Advanced age does not appear to clinically impact rabeprazole's metabolism.<sup>[14]</sup> However, elevations in the maximum plasma concentration and the total drug exposure ([area under the curve](#), AUC) have occurred.<sup>[1]</sup>

### Japanese ancestry

In a study on rabeprazole's [pharmacokinetics](#), the AUC was elevated by approximately 50–60% in healthy [Japanese](#) men compared to healthy men in the United States.<sup>[15]</sup> See the pharmacogenetics section below for a pharmacogenetic explanation of these findings.

### Renal or hepatic impairment

In people that have renal or hepatic impairment, these problems do not appear to affect rabeprazole's metabolism in a clinically meaningful way. This includes individuals on [dialysis](#). Severe liver insufficiency, such as during [cirrhosis](#), does affect rabeprazole's elimination half-life, but not to a degree of dangerous accumulation.<sup>[14]</sup> In a review of patients taking rabeprazole while having [end-stage kidney disease](#) and mild-to-moderate severity, chronic compensated cirrhosis of the liver, the alteration in rabeprazole's metabolism was not clinically meaningful.<sup>[8]</sup>

## Contraindications

Rabeprazole should not be used in the following populations and situations:<sup>[7]</sup>

- people with a known hypersensitivity (allergy) to rabeprazole, substituted [benzimidazoles](#) (which are chemically similar to rabeprazole, like [omeprazole](#)), or any other component of the capsule formulation (e.g. certain dyes)
- concurrent use of [rilpivirine](#), a medication used to treat [HIV](#) infection

## Hypersensitivity

### Syndrome

An allergy to a PPI like rabeprazole may take the form of [type I hypersensitivity](#) or [delayed hypersensitivity](#) reactions. A selective (pattern C — see below for a discussion of cross-reactivity patterns) type I hypersensitivity reaction to rabeprazole resulting in [anaphylaxis](#) has

been reported, as well as several whole group hypersensitivities.<sup>[16]</sup>

### Cross-reactivity

Hypersensitivity to PPIs can take the form of whole group hypersensitivity, pattern A, B, or C. Whole group hypersensitivity occurs when a person is cross-reactive to all PPIs; that is, all PPIs will induce the allergy. In pattern A, a person may be allergic to omeprazole, esomeprazole, and pantoprazole, but not to lansoprazole and rabeprazole. This is thought to be due to the structural similarities between omeprazole, esomeprazole, and pantoprazole, contrasted with lansoprazole and rabeprazole. Pattern B is the opposite, reflecting people that are allergic to lansoprazole and rabeprazole, but not to omeprazole, esomeprazole, and pantoprazole. Pattern C, in the context of rabeprazole, would reflect a person that is allergic to only rabeprazole, but not to other PPIs (omeprazole, esomeprazole, pantoprazole, and lansoprazole).<sup>[16]</sup>

### Contraindication with rilpivirine

Rilpivirine, a [non-nucleoside reverse transcriptase inhibitor](#) (NNRTI) used in the treatment of HIV, is contraindicated with all PPIs because of their acid-suppressing effect. PPIs suppress acid, thereby raising the pH of (alkalizing) the stomach's contents. Rilpivirine is best absorbed under acidic conditions. Therefore, rabeprazole would be expected to decrease the absorption of rilpivirine, decrease the concentration of rilpivirine in the blood, and possibly lead to therapeutic failure and induce resistance of the HIV virus to rilpivirine and/or cross-resistance with other NNRTIs.<sup>[17]</sup>

## Adverse effects

In general rabeprazole is fairly well tolerated, even with up to 5 years of continuous use (the duration of follow-up in a [pharmacovigilance](#) clinical trial<sup>[18]</sup>).<sup>[8]</sup> The [side effect](#) profile is similar to that of [omeprazole](#) and other commonly used PPIs.<sup>[14]</sup> The most common side effects include [headache](#), [nausea](#), and [diarrhea](#).<sup>[8]</sup> Rare side effects include rashes, flu-like symptoms, and infections (including by the gastrointestinal pathogen [Clostridium difficile](#)<sup>[19]</sup>).<sup>[14]</sup> Rare instances of rabeprazole-induced [liver injury](#) (also known as hepatotoxicity) have been reported. Characteristic proton-pump inhibitor hepatotoxicity occurs within the first 4 weeks of starting the medication.<sup>[20]</sup>

[Gastrin](#) is an endogenous human hormone that stimulates gastric acid secretion and regulating the growth of certain cells in the stomach.<sup>[21]</sup> [Enterochromafin-like](#)



(ECL) cells, responsible for stimulating gastric acid secretion by the release of [histamine](#) in the stomach, respond to prolonged gastrin exposure by growing and proliferating.<sup>[21]</sup> Rabepazole is associated with elevated serum gastrin levels (hypergastrinemia), which occurs through inhibiting the negative feedback of stomach acid on gastrin secretion by [G cells](#) in the [antrum](#) of the stomach.<sup>[21]</sup> The elevation in serum gastrin levels are thought to be dependent upon the degree of rabepazole's [CYP2C19](#) metabolism. Rabepazole is not as significantly metabolized by CYP2C19 compared to other medications in the same class, like omeprazole.<sup>[8]</sup> Hypergastrinemia has been posited as a potential source of rabepazole-induced neuropsychiatric symptoms (e.g. dizziness, numbness, and tremor), though more research is needed to clarify the effect and mechanism.<sup>[22]</sup>

Prolonged elevated serum gastrin has been shown to cause rat ECL cells to form [carcinoid tumors](#).<sup>[21]</sup> According to a 2013 meta-analysis of observational studies, the use of acid-suppressing drugs (including PPIs like rabepazole, but also [histamine receptor 2 antagonists](#)) may be associated with the development of gastric cancer.<sup>[23]</sup> The studies included in the meta-analysis did not differentiate between rabepazole and other PPIs,<sup>[24][25][26][27]</sup> so it is unclear if the potential risk may differ across the PPI class.

Acid suppression via rabepazole can decrease the absorption of [vitamin B12](#) and [magnesium](#), leading to deficiency.<sup>[7]</sup> A case of rabepazole-induced [iron deficiency anemia](#) has been reported.<sup>[28]</sup> Theoretically, rabepazole could induce an iron deficiency anemia by reducing the dietary absorption of iron, which requires acid for bioavailability.<sup>[28]</sup>

Very serious side effects have been reported in people taking rabepazole, but there is no direct evidence that rabepazole definitely caused these side effects.<sup>[1]</sup> These include [Stevens-Johnson syndrome](#) (a serious disease characterized by skin rash and risk of organ failure), serious [blood cell](#) abnormalities, coma, and death.<sup>[1]</sup> Other possible side effects, common to other PPIs medications in the same class, include bone fractures due to [osteoporosis](#), serious infections (including [Clostridium difficile](#)), and kidney damage (nephrotoxicity).<sup>[7]</sup> A rare, though less understood, side effect of the PPI class is the risk of [myopathy](#) and [rhabdomyolysis](#), a syndrome of striated muscle destruction.<sup>[29]</sup>

## Osteoporosis and fractures

The mechanism of PPI-induced osteoporosis and fractures is unclear, but hypotheses include hypocalcemia and hypomagnesemia, hyperparathyroidism, and B12

deficiency (inducing neurological deficits and subsequent falls).<sup>[30]</sup> In opposition to the calcium malabsorption hypothesis, rabepazole prevented reductions in [bone mineral density](#) akin to the effect of [minodronic acid](#) in a study of [gastrectomized rats](#).<sup>[31]</sup> Midodronic acid is a [bisphosphonate](#) class drug used to prevent fractures in osteoporosis.<sup>[32]</sup> Unlike midodronic acid, rabepazole did not affect serum calcium levels, although the attenuation of gastrectomy-induced bone mineral density reduction at the distal end of the femur suggested inhibition of bone resorption by [osteoclasts](#) (like a bisphosphonate).<sup>[31]</sup>

## Infection risk

PPIs have been associated with an increased risk for [pneumonia](#) by [meta-analyses](#)<sup>[33][34][35]</sup> of case-control and cohort studies.<sup>[36]</sup> One hypothesis for this association is that PPI-induced acid suppression fosters the growth of aerobic bacteria in the stomach, which can be transferred to the lungs by [microaspiration](#), promoting [colonization](#) and subsequent pneumonia.<sup>[36]</sup> Other hypotheses include off-target proton pump inhibition in the lungs, altering the pH of pulmonary mucus in favor of bacterial growth, and direct inhibition of the activity of white blood cells such as [neutrophils](#) and [natural killer cells](#).<sup>[35]</sup> In line with the stomach acid suppression hypothesis for bacterial overgrowth, PPIs have also been associated with [Clostridium difficile](#) infections.<sup>[36]</sup> However, as these meta-analyses have pooled PPIs together, it is unknown whether the risk of infection differs significantly between rabepazole and other members of the PPI class.<sup>[36]</sup> Rabepazole was identified as the causative agent in a case report collagenous colitis, inducing chronic, watery diarrhea.<sup>[37]</sup>

Other enteric, infectious organisms associated with PPI use include [Campylobacter](#) and [Salmonella](#).<sup>[38]</sup> Both pathogens are sensitive to acid;<sup>[39]</sup> theoretically, as above, acid suppression by PPIs should increase their [pathogenicity](#). It is unclear if the observed association is due to the PPI itself, as one cohort study found that the association could be explained by the demographic factors of patients prescribed PPIs (e.g. concurrent use of immunosuppressant medications, older age, and antibiotic use).<sup>[40]</sup> In a clinical trial of 255 Japanese patients, the incidence of PPI-associated diarrhea did not differ between rabepazole, omeprazole, or lansoprazole.<sup>[41]</sup>

## Nephrotoxicity

Forms of kidney damage associated with PPIs in one meta-analysis include [acute interstitial nephritis](#) (AIN) (insufficient quality evidence), [acute kidney injury](#) (AKI) (low grade evidence), [chronic kidney disease](#) (CKD) (low



grade evidence), and **end-stage renal disease** (insufficient quality evidence).<sup>[42]</sup> The first reported case of rabeprazole-induced AIN occurred in a 62 year-old female in Australia, prescribed rabeprazole for complaints of dyspepsia due to suspected GERD.<sup>[43]</sup> The mechanism for PPI-induced AIN has not been elucidated, though an immune-related hypothesis has been posited on the basis of extra-renal toxicity consistent with an immunologic, **hypersensitivity** reaction.<sup>[43]</sup> It has also been posited that incomplete resolution of PPI-induced AIN could precede AKI and CKD.<sup>[42]</sup>

## Muscle-related adverse events

Cases of progressive muscle weakness, muscle pain, and rhabdomyolysis following administration of PPIs have been reported in the scientific literature.<sup>[29]</sup> However, the mechanism for these muscle-related adverse events has yet to be established.<sup>[29]</sup> In one case, rhabdomyolysis developed in a 50 year-old patient 2 weeks after starting both rabeprazole and **domperidone**, a prokinetic and antiemetic agent,<sup>[44]</sup> which resolved after discontinuation of both drugs.<sup>[29]</sup> Per the French imputability method of causality assessment, it was determined that rabeprazole was a "plausible" cause of the rhabdomyolysis, noting that domperidone was started concurrently.<sup>[29]</sup>

## Overdose

No signs and symptoms have been reported in overdoses of rabeprazole up to 80 mg, but case examples are limited.<sup>[45]</sup> Notably, rabeprazole has been used in higher doses for the treatment of hypersecretory conditions like Zollinger-Ellison syndrome (up to 120 mg daily).<sup>[45]</sup>

Animal experiments with ultra-high doses of rabeprazole have demonstrated lethality through unknown mechanisms. The lethal overdose syndrome in animals is characterized by convulsion and coma.<sup>[15]</sup>

## Interactions

### Drug-drug interactions

Rabeprazole does not interfere with the plasma concentration of drugs that are also metabolized by the same enzymes (i.e. CYP2C19) that it is metabolized by. Therefore, it is not expected to react with CYP2C19 substrates like **theophylline**, **warfarin**, **diazepam**, and **phenytoin**.<sup>[14]</sup>

Clinically serious drug-drug interactions may involve the acid-suppression effects of rabeprazole. For example, rabeprazole should not be used concomitantly with **rilpivirine**, an anti-HIV therapy, which requires acid for absorption. Lowered plasma concentrations of rilpivirine could lead to progression of HIV infection. Other drugs that require acid for absorption include **antifungal drugs** like ketoconazole and **itraconazole**, **digoxin**, **iron**, **mycophenolate**, and **tyrosine kinase inhibitors** like **erlotinib**, **dasatinib**, and **nilotinib**.<sup>[7]</sup> There are no clinically relevant drug interactions between rabeprazole and antacids.<sup>[8][15]</sup>

There is some evidence that **omeprazole** and **esomeprazole**, two medications in the same class as rabeprazole, can disturb the conversion of an **anticoagulant** medication called **clopidogrel** to its active metabolite. Still, whether the effect of omeprazole and esomeprazole on clopidogrel's metabolism actually leads to poor clinical outcomes is still a matter of intense debate among healthcare professionals.<sup>[8]</sup> However, because this is thought to be mediated by the effect of omeprazole and esomeprazole on CYP2C19, the enzyme that activates clopidogrel, this drug interaction is not expected to occur as strongly with rabeprazole.

### Food-drug interactions

Food does not affect the amount of rabeprazole that enters the body,<sup>[8]</sup> but it does delay its onset of effect by about 1.7 hours.<sup>[14]</sup>

## Pharmacology

### Mechanism of action

Once rabeprazole is taken by mouth, the enteric coating of the tablet allows the drug to pass through the stomach intact.<sup>[15]</sup> Like other PPIs, rabeprazole is absorbed into the blood stream at the site of the proximal small bowel.<sup>[46]</sup> Rabeprazole's molecular mechanism of action involves crossing from the blood stream into the **parietal cells** of the **stomach**, which are the cells that are responsible for secreting **hydrochloric acid** (HCl).<sup>[1]</sup> At this point, rabeprazole is inactive.<sup>[1]</sup> However, rabeprazole is then secreted into the **secretory canaliculus** of the parietal cells, which is the space from which acid secretion occurs.<sup>[1]</sup> Here, acid secretion is mediated by the energy-dependent acid pumps, called **hydrogen potassium adenosine triphosphatase** (H<sup>+</sup>/K<sup>+</sup> ATPase) pumps.<sup>[1]</sup> These **enzymatic** pumps have **cysteine amino acid** residues.<sup>[1]</sup> After being activated by gastric (stomach) acid to a reactive **sulfenamide** intermediate,<sup>[47]</sup> rabeprazole permanently binds the cysteine residues,



forming [covalent, disulfide bonds](#).<sup>[1]</sup> This action fundamentally alters the configuration of the acid pump, thereby inhibiting its activity. Thus, acid can no longer be secreted into the gastric lumen (the empty space of the stomach), and the [pH](#) of the stomach increases (decrease in the concentration of hydrogen ions,  $H^+$ ).<sup>[1]</sup> Due to the permanent inhibition of the individual proton pump that each molecule of rabeprazole has bound to, acid secretion is effectively suppressed until new proton pumps are produced by the parietal cells.<sup>[20]</sup>

Rabeprazole, like other medications in the same class, cannot inhibit the  $H^+/K^+$  ATPase pumps found in [lysosomes](#), a cellular organelle that degrades biological molecules, because the pumps found in these organelles lack the cysteine residues involved in rabeprazole's mechanism of action.<sup>[8]</sup>

A unique feature of rabeprazole's mechanism of action in inhibiting acid secretion involves its activation. The [pKa](#) (the pH at which 50% of the drug becomes positively charged) of rabeprazole is around 5.0, meaning that it doesn't take a lot of acid to activate it. While this theoretically translates into a faster onset of action for rabeprazole's acid-inhibiting effect, the clinical implications of this fact have yet to be elucidated.<sup>[1]</sup> Theoretically, a high pKa should correlate with off-target activation of the PPI (possibly inducing side effects), though the clinical relevance of this has also yet to be elucidated.<sup>[48]</sup> See [Table 1](#) for a pKa comparison across PPIs.

**Table 1** | Comparative pKa values across PPIs. Note that the pKa of dexlansoprazole is a calculated value from a different source, which may have used differing methods than the other PPIs studied.

Proton pump inhibitor pKa <sup>[48]</sup>			
<b>PPI</b>	<b>Omeprazole</b>	<b>Esomeprazole</b>	<b>Lansoprazole</b>
<b>pKa</b>	4.13	4.13	4.01
<b>PPI</b>	<b>Dexlansoprazole</b>	<b>Pantoprazole</b>	<b>Rabeprazole</b>
<b>pKa</b>	9.35 <sup>[49]</sup>	3.96	4.90

## Pharmacokinetics

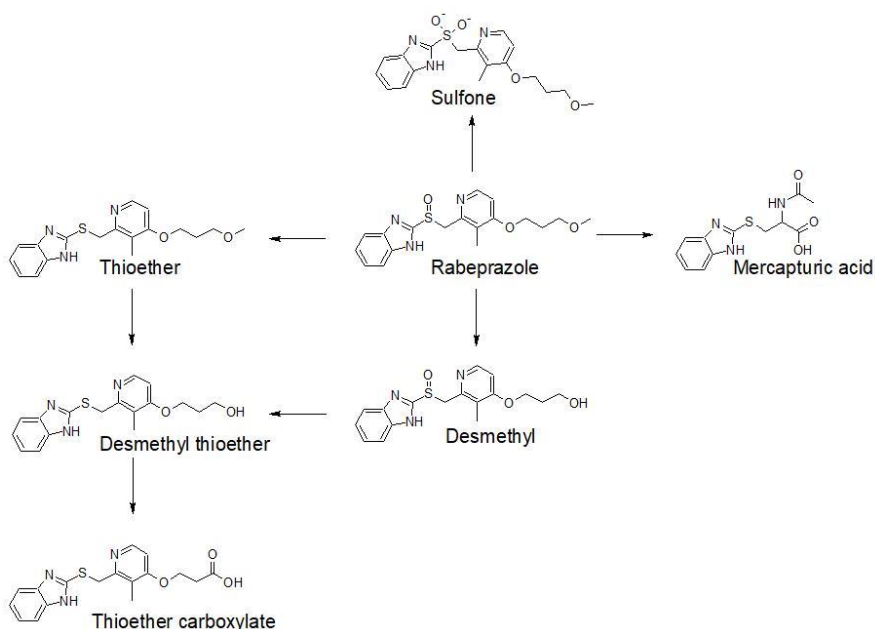
Rabeprazole's bioavailability is approximately 52%, meaning that on average 52% of orally administered dose is expected to enter systemic circulation (the bloodstream).<sup>[1]</sup> Once in the blood, rabeprazole is approximately 96.3%<sup>[14]</sup>-97%<sup>[8]</sup> bound to plasma proteins. The biological [half-life](#) of rabeprazole in humans is approximately 1 hour.<sup>[8]</sup> It takes about 3.5 hours for rabeprazole to reach the maximum concentration in human plasma after a single orally administered dose. Oral absorption is independent of the dose administered.<sup>[8]</sup>

Rabeprazole is extensively metabolized by the [liver](#).<sup>[14]</sup> 90% of the drug is rendered into metabolites by the liver, which are then excreted by the [kidneys](#).<sup>[45]</sup> 10% of the dose is excreted in the feces.<sup>[8]</sup> The drug metabolizing enzymes primarily responsible for rabeprazole's metabolism are [CYP2C19](#) and [CYP3A4](#).<sup>[14]</sup> However, rabeprazole is mainly metabolized through non-enzymatic [reduction](#) to a thioether metabolite.<sup>[8]</sup> Some of rabeprazole's metabolites include the following: a [thioether carboxylic acid](#) metabolite, a thioether [glucuronide](#) metabolite, and a [sulfone](#) metabolite.<sup>[14]</sup> The most common metabolites excreted in the urine are the mercapturic acid conjugate and carboxylic acid.<sup>[8]</sup> A diagram of rabeprazole's [phase I metabolism](#) is shown in [Figure 3](#).

## Pharmacogenetics

The effect of rabeprazole may [vary based upon the genetics](#) of the individual taking the medication. People may have differences in their capacity to metabolize rabeprazole to an inactive metabolite. This may be mediated through genetic differences in the gene that encodes for the metabolic enzyme [CYP2C19](#). For example, people that are poor CYP2C19 metabolizers (i.e. their version of CYP2C19 is less effective than average) will have trouble metabolizing rabeprazole, allowing the active rabeprazole to stay in the body, where it can exert its effect, longer than intended. Conversely, extensive CYP2C19 metabolizers (i.e. the average metabolic capacity of CYP2C19) will extensively metabolize rabeprazole, as expected. The poor metabolizing CYP2C19 [phenotype](#) is found in roughly 3–5% of [Caucasian](#) people, and in 17–20% of people of [Asian](#) ancestry.<sup>[50]</sup> In a study on men of [Japanese ancestry](#), this has translated to an average increase of total drug exposure by 50–60% compared to men in the United States.<sup>[15]</sup>

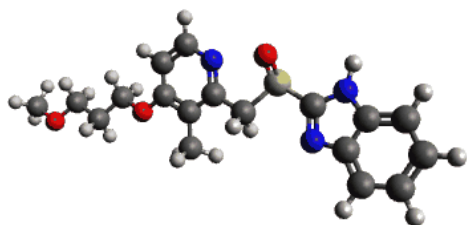
However, rabeprazole's metabolism is primarily non-enzymatic (it is often inactivated chemically, without the participation of the body's natural drug metabolizing [enzymes](#)). Therefore, while a person's CYP2C19 phenotype will affect rabeprazole's metabolism, it is not expected to dramatically affect the efficacy of the medication.<sup>[8]</sup>



**Figure 3** | Phase I metabolism of rabeprazole,<sup>[15]</sup> drawn in ChemSketch. Rabeprazole can be initially metabolized to one of four metabolites. The thioether and desmethyl metabolites can be further metabolized to a common desmethyl thioether metabolite, and then a thioether carboxylate metabolite. *Joseph Cusimano, CC-BY-SA 4.0*

## Chemistry

Rabeprazole, represented in 3D in **Figure 4**, is classified as a substituted benzimidazole, like omeprazole, lansoprazole, and pantoprazole.<sup>[47]</sup> Rabeprazole possess properties of both acids and bases, making it an amphotere.<sup>[47]</sup> The acid dissociation constant ( $pK_a$ ) of the pyridine nitrogen is about equal to 4.<sup>[47]</sup>



**Figure 4** | Representation of rabeprazole (Click on the figure to access the 3D representation of rabeprazole spinning along an axis). *Joseph Cusimano, CC-BY-SA 4.0*

## Synthesis

The synthesis pathway in **Figure 5** begins with 2,3-dimethylpyridine *N*-oxide (**1**). Nitration of 2,3-dimethylpyridine *N*-oxide affords the nitro derivative (the addition of  $NO_2$ ) (**2**) The newly introduced nitro group is

then displaced by the alkoxide from 3-methoxypropanol to yield the corresponding ether (**3**). Treatment with acetic anhydride results in the Polonovski reaction. Saponification followed by treatment with thionyl chloride then chlorinates the primary alcohol (**5**). Reaction with benzimidazole-2-thiol (**6**) followed by oxidation of the resulting thioether to the sulfoxide yields the final product: rabeprazole (**8**).<sup>[51][52]</sup>

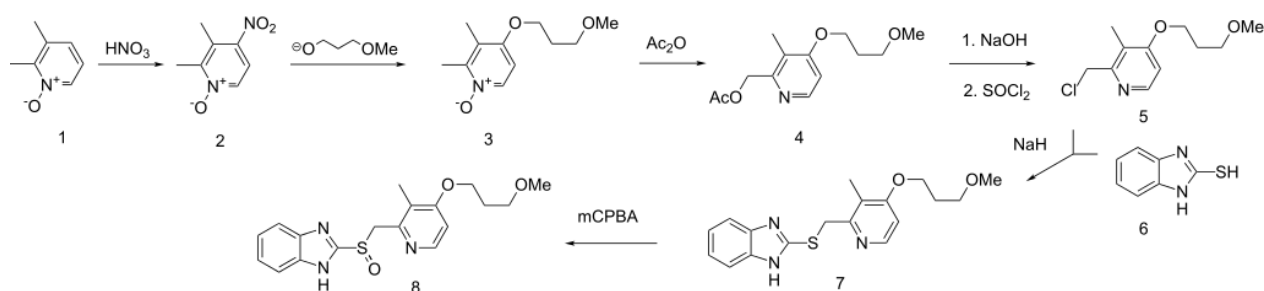


Figure 5 | Rabeprazole synthesis diagram.<sup>[51][52]</sup> Nuklear, CC-BY-SA 4.0

## Comparative chemistry

The chemical structures in **Table 2** illustrate the comparative chemistry of rabeprazole among other members of the PPI class. The structures vary by the substitution of side chains on either the **benzimidazole** or **pyridine** ring structures. Omeprazole, for example, has a **methoxy moiety** (CH<sub>3</sub>O-) on the benzimidazole ring at position 5, whereas pantoprazole has a difluoromethoxy (CHF<sub>2</sub>O-) chain at position 5. Lansoprazole has a trifluoroethoxy (CF<sub>3</sub>-CH<sub>2</sub>-O-) chain on the pyridine ring at position 4, whereas rabeprazole has a methoxypropoxy

(CH<sub>3</sub>-O-(CH<sub>2</sub>)<sub>3</sub>-O-) chain at position 4.<sup>[16]</sup> Esomeprazole and deslansoprazole represent **stereoisomers** of omeprazole and lansoprazole respectively.<sup>[53][54]</sup>

## Physicochemical properties

Rabeprazole is characterized as a white to yellowish-white solid in its pure form. It is soluble in a number of **solvents**. Rabeprazole is very soluble in water and **methanol**, freely soluble in **ethanol**, **chloroform**, and **ethyl acetate**, and is insoluble in **ether** and **n-hexane**.<sup>[15]</sup> It is unstable under humid conditions.<sup>[8]</sup>

Table 2 | Comparative chemical structures of commercially available PPIs.

PPI	Omeprazole	Esomeprazole	Lansoprazole
Chemical structure			
PPI	Dexlansoprazole	Pantoprazole	Rabeprazole
Chemical structure			

## History

Rabeprazole was first marketed in Europe in 1998.<sup>[8]</sup> In 1999, one year later, rabeprazole was approved for use in the **United States**.<sup>[19]</sup>

## Development

Developed by **Eisai Medical Research** under the research names E3810 and LY307640, the pre-investigational new drug application was submitted on October

28, 1998. The final investigational **new drug application** was submitted August 6, 1999. On August 19, 1999, rabeprazole was approved in the US for multiple gastrointestinal indications. The approval for the treatment of symptomatic **gastroesophageal reflux disease** was on February 12, 2002.<sup>[5]</sup>





## Society and culture

### Legal status

Rabeprazole is approved in the [United States](#)<sup>[55]</sup> and the [United Kingdom](#)<sup>[56]</sup> for [prescription use only](#). Rabeprazole was approved in [India](#) in December 2001.<sup>[57]</sup> It was approved in [Japan](#) in 1997, and in all [European Union](#) member countries since.<sup>[58]</sup>

### Brand names

Rabeprazole has been sold in a number of brand names:<sup>[59]</sup>

Table 3 | List of [trade names](#) for rabeprazole.<sup>[59]</sup>

Alphabet	Brand Name
A	Acera, Acifix, Acilesol, AcipHex, Acistal, Akirab, Algibra, An Si Fei, Anslag, Antuc, Apt, Aurizol-R
B	Bacanero, Barole, Bauzole, Bepa, Bepraz, Berazol, Berizar, Beryx
C	Cyra
D	Dexicool, Dexpure, Dirab, Domol
E	Eurorapi
F	Finix, Fodren
G	Gastech, Gastrazole, Gastrodine, Gelbra
H	Happi, Helirab, Heptadin
I	Idizole
J	Jelgrade, Ji Nuo
K	
L	
M	Mergium, Monrab
N	Neutracaïne, Newrabbell, Noflux
O	Olrite, Ontime, Oppi-R
P	Paliell, Paramet, Paricel, Pariet, Pepcia, Pepraz, Ppbest, Praber, Prabex, Prabexol, Prabez, Promto, Pulos
Q	
R	R-Bit, R-Cid, R-PPI, R-Safe, R.P.Zole, Rabby, Rabe, Rabe-G, Rabeact-20, Rabec, Rabeca, Rabecell, Rabecis, Rabecole, Rabecom, Rabecon, Rabee, Rabefine, Rabegen, Rabekind, Rabelex, Rabelinz, Rabelis, Rabeloc, Rabeman, Rabemed, Rabeol, Rabeone, Rabep, Rabepazole, Rabephex, Rabeprazol, Rabeprazole, Rabeprazolo, Rabeprazolum, Rabesec, Rabestad, Rabetac, Rabetome, Rabetra, Rabetune, Rabeum, Rabex, Rabez, Rabez-FR, Rabezol, Rabezole, Rabibit, Rabicent, Rabicid, Rabicip, Rabifar, Rabifast, Rabilect, Rabip, Rabipot, Rabirol, Rabitab, Rabium, Rabiza, Rabizol, Rablet, Rablet-B, Rabon, Raboz, Rabroz, Rabyprex, Ragi, Ralic, Ramprozole, Raneks, Rap, Rapeed, Rapespes, Rapo, Rapoxol, Rasonix, Razid, Razit, Razo, Razodent, Razogard, Rebacip, Redura, Reorab, Reward, Rifcid, Rodesa, Rolant, Roll, Rowet, Rpraz, Rui Bo te, Rulcer
S	Setright, Staycool, Stom, Stomeck
T	
U	Ulceprazol, Ulcerostate
V	Value, Veloz
W	Wowab
X	Xin Wei An
Y	Yu Tian Qing
Z	Zibepar, Zolpras, Zulfex

Table 4 | List of [trade names](#) for rabeprazole-containing combination products.<sup>[59]</sup>

Generic Combination	Brand Name
rabeprazole, amoxicillin, clarithromycin	Rabecure, Pylocure
rabeprazole, amoxicillin, metronidazole	Rabefine
rabeprazole, diclofenac	Drab, Rabin-DFX, Rclonac, Safediclo, Samurai
rabeprazole, domperidone	Acera-D, Acistal-D, Adec-R, Algibra-D, Anslag-D, Antuc-DSR, Biorab-DSR, Catrab-DSR, Comvine, Cyclochek, Cyra-D, Dirab-D, Domol-R, Esoga-RD, Gasonil-D, Gastrazole-D, Happi-D, Helirab-D, Kurab-DSR, Lorab-DSR, Neutraflux, Nuloc-D, Olrite-DSR, Parisec-DSR, Pepchek, Pepcia-D, Peraz-D, Ppbest-D, Prazim-RD, Prorab-D, R-Bit-DM, R-Bit-DSR, R-Cid Plus, R-DSR, R-Safe DSR, Rabby-DSR, Rabecis-DSR, Rabecom-D, Rabecon-DSR, Rabee-D, Rabefine-DSR, Rabelex-D, Rabemac-DSR, Rabep-DSR, Rabephex-D, Rabetome-DM, Rabetome-DSR, Rabetune-D, Rabex-D, Rabez-D, Rabi-DSR, Rabibit-D, Rabicent-D, Rabicip-D, Rabifast-DSR, Rabilect-DSR, Rabipot-D, Rabiprime-DSR, Rablet-D, Rabon-D, Rabon-DSR, Rabroz-DSR, Rabter-SR, Raizol-DSR, Rap-D, Rapeed-D, Rapo-DSR, Raz-DSR, Rebilex-DSR, Redoxid, Redura-D, Redura-DSR, Reorab-D, Reorab-DSR, Reward-D, Reward-DSR, Rifcid-D, Rifcid-DSR, Rifkool-DSR, Robilink-D, Rolant-D, Roll-D, Rpraz-D, Rugby-DM, Rulcer-DSR, Setright-DSR, Sharaz-D, Staycool-DXR, Stomeck-D SR, Ulgo-DSR, Xenorab-DSR, Zolorab-D, Zomitac-DSR, Zorab-D
rabeprazole, itopride	Acera-IT, Antuc-IT, Cool Rab-IT, Happi-IT, Itopraz, Itorab, Jeprab-ITO, Pepraz-I, Rabee-ISR, Rabemac-ITR, Rabetome-ISR, Rabez-IT, Rabibit-ISR, Rablet-I, Rablet-IT, Rebilex-ISR, Reorab-IT, Rex-ISR, Rulcer-IT, Veloz-IT, and Zorite
rabeprazole, lafutidine	Lafumac Plus
rabeprazole, levosulpiride	Happi-L, Lorab-L, Rabekind Plus, Rabicent-L, Rabifast-XL, Rabin-LXR, Rabinta-L, Rabitem-LS, Robiwell-L, Roll-LS, Wokride
rabeprazole, ondansetron	Ond-R, Rulcer-ON
rabeprazole, polaprezinc	Happi-XT, Rabez-Z
rabeprazole, sodium bicarbonate	Pepcia-FF, Raizol

## Research

An alternative formulation of rabeprazole, termed "rabeprazole-ER" (extended release) has been developed. The purpose of the formulation was to increase the half-life of rabeprazole, which normally is very short in humans. Rabeprazole-ER was a 50 mg capsule composed of five non-identical 10 mg tablets that were designed to release rabeprazole at differing intervals throughout



the gastrointestinal system. However, because two high quality clinical trials<sup>[60]</sup> failed to demonstrate a benefit of rabeprazole-ER versus esomeprazole (another common PPI) for healing grade C or D erosive esophagitis, the development of rabeprazole-ER ceased.<sup>[46]</sup>

## Additional information

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