Proton pump inhibitors (PPIs) are highly effective drugs for treatment of gastric acid-related disorders. Omeprazole, pantoprazole, lansoprazole, rabeprazole and esomeprazole, the S-isomer of omeprazole, are currently approved for clinical use. Although PPIs are often thought to be interchangeable, differences have emerged in their pharmacological profiles, which may be reflected in relevant aspects of their clinical efficacy. All PPIs share the ability to inhibit acid secretion via blockade of gastric proton pump ($\text{H}^+\text{K}^+$-ATPase). Proton pump inhibition requires accumulation of PPIs in the acid environment of secretory canalicula of parietal cells, followed by acid-mediated conversion into active derivatives and binding to cysteine residues of $\text{H}^+\text{K}^+$-ATPase. However, PPIs are endowed with different physicochemical properties, resulting in pharmacodynamic differences which influence their anti-secretory potency, speed of activation, and duration of acid inhibition. For instance, pantoprazole is activated more slowly than other PPIs, while rabeprazole is characterized by a rapid onset of action combined with a faster recovery of proton pump function. Key pharmacokinetic parameters (i.e., $T_{\text{max}}$ and elimination $t_{1/2}$) do not differ appreciably among PPIs. However, differences in the hepatic metabolism can produce inter-patient variability in acid suppression and clinical efficacy, since the pharmacodynamic response to PPIs is closely related to their area under curve (AUC) of the anti-secretory effect versus time. PPIs are metabolized by CYP2C19 in the liver, and genetic variations of this enzyme result in impaired metabolism which gives rise to three distinct phenotypes: fast, medium and slow metabolizers. Accordingly, the incidence of mutant alleles in a patient population under treatment with PPIs for acid-related disorders can influence the clinical outcomes. For instance, therapeutic failures can occur in rapid metabolizers, who have less available drug to inhibit proton pumps. Approaches to this problem include patient’s genotyping prior to start treatment in order to tailor dose regimens to the individual metabolic capacity. An alternative option is the development of PPIs less susceptible to inter-individual genetic variations of hepatic metabolic pathways. In line with this strategy, esomeprazole has been developed owing to its ability to inhibit CYP2C19, thus reducing its own hepatic metabolism. Such a property is mostly relevant in medium/rapid metabolizers (about 93% of Caucasians) who, as a consequence of esomeprazole-induced CYP2C19 inhibition, behave as slow metabolizers, with a significant reduction of their inter-individual variability to the pharmacological blockade of gastric acid secretion.