THE PACKAGE INSERT SERIES

Proton Pump Inhibitors — The Drug You Can't Stop Taking

BY

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The Prilosec label indicates the drug for short-term treatment of duodenal ulcer, gastric ulcer, GERD and erosive oesophagitis — four to eight weeks. Efficacy beyond eight weeks "has not been established". For maintenance of healing, the label adds that controlled studies do not extend beyond 12 months. The drug has been on the US market since 1989. Tens of millions of Americans take it every day, many of them for years.

> *The Protonix label, in section 5.6 Tumorigenicity, states that pantoprazole was carcinogenic in long-term rodent studies and caused rare gastrointestinal tumours. The relevance to humans, the same section says, is unknown. The Prilosec and Nexium labels report a parallel finding for omeprazole — gastric carcinoid tumours and ECL cell hyperplasia in 24-month rat studies, dose-related, more frequent in females. All three labels describe the class effect: the drugs raise serum gastrin, gastrin drives ECL cell proliferation, and in rodents this proceeds to tumours. The Prilosec label adds that the human studies done so far were of insufficient duration and size to settle the carcinogenicity question. The drug is approved for short-term use. The carcinogenicity question depends on long-term use.*

The Prilosec label also states that omeprazole produced "a significant increase in the intragastric concentrations of viable bacteria" — a direct admission that suppressing stomach acid changes which organisms the stomach harbours. The Protonix label warns of B-12 malabsorption with use longer than three years. All three PPI labels carry warnings for hypomagnesaemia, bone fracture, atrophic gastritis, fundic gland polyps, interstitial nephritis, and Clostridium difficile-associated diarrhoea. None of these warnings appeared on the original 1989 approval. Each was added later.

The Package Insert reads what the FDA-approved prescribing information says about the most commonly prescribed drugs in the United States. This installment draws on the labels for omeprazole (Prilosec) — the original PPI; pantoprazole (Protonix); esomeprazole (Nexium) — the s-isomer of omeprazole, approved as a separate drug; and famotidine (Pepcid) — the older H2 blocker class that PPIs largely displaced. Lansoprazole (Prevacid) and rabeprazole (Aciphex) are also widely prescribed PPIs in the same class; the findings below are class effects and apply to them as well. If you are currently taking a PPI, considering one, or have a family member on one, this is the installment to start with.

The trap by design

The Prilosec label, in the section on pharmacodynamics, describes what the drug does and what happens when it stops.

The drug binds covalently to the H+/K+ ATPase enzyme on the gastric parietal cell — the final pump in acid production. Inhibition is dose-dependent. After a 40 mg dose, the label reports peak inhibition reaching 94% of basal acid output. With daily dosing, inhibition reaches a plateau after four days. When the drug is stopped, the label states, secretory activity returns gradually over 3 to 5 days. The same label, two paragraphs later, describes what happens to serum gastrin during this process: levels rise over the first 1-2 weeks of dosing, plateau, and return to pretreatment levels within 1 to 2 weeks after the drug is discontinued.

The combination is the trap.

Acid secretion is suppressed by 80-94%. Gastrin — the hormone that signals the stomach to produce acid — rises in response to the suppression. The body, sensing low acid, instructs the parietal cells to compensate. The drug blocks that compensation as long as it is taken. When the drug is stopped, the gastrin signal is still elevated, and the parietal cells are no longer blocked. The result is a period during which acid production rebounds above the patient's baseline. The patient experiences this as the original heartburn returning, often worse. The patient takes the drug again. The cycle restarts.

The Protonix label is the only one of the three PPI labels to use the word “rebound”. It reports a 7-day dosing study in healthy volunteers in which acid secretion returned to normal within a week of the last dose, with no evidence of rebound hypersecretion. The study was 7 days long. The clinical question — what happens after 7 months or 7 years — is not addressed. The other two PPI labels do not use the term at all. They describe the gastrin elevation, the ECL cell hyperplasia and the secretory return without naming what happens during that return.

> ASK YOUR DOCTOR
> *If gastrin levels rise during PPI treatment and acid secretion is suppressed by 80-94%, what is the expected acid output during the days after I stop taking this drug?*

The carcinogenicity question the labels do not resolve

The Nexium label, in section 13.1 on nonclinical toxicology, reports the rat carcinogenicity studies in detail. At doses ranging from 1.7 to 141 mg/kg/day — about 0.7 to 57 times the human dose on a body surface area basis — omeprazole produced gastric ECL cell carcinoid tumours in a dose-related manner. The incidence was markedly higher in female rats, which had higher blood levels of the drug. ECL cell hyperplasia was present in all treated groups of both sexes. Gastric carcinoids, the label notes, seldom occur in untreated rats.

Section 5.6 Tumorigenicity on the Protonix label is more direct. It states that pantoprazole was carcinogenic in long-term rodent studies, that the tumours observed were rare types of gastrointestinal tumours, and that the relevance to humans is unknown. The nonclinical section adds detail. Pantoprazole produced ECL cell hyperplasia and benign and malignant neuroendocrine cell tumours in the gastric fundus of Sprague-Dawley rats at doses as low as 0.5 mg/kg/day — about 0.1 times the human dose. At higher doses, the same study found benign and malignant squamous cell carcinomas in the forestomach, hepatocellular adenomas and carcinomas in the liver, and follicular cell adenomas and carcinomas in the thyroid. Pantoprazole was also positive in human lymphocyte chromosomal aberration assays, in one of two mouse micronucleus tests for clastogenic effects, and in a Chinese hamster ovarian cell forward mutation assay for mutagenic effects.

For human data, the Prilosec label points to gastric biopsies from more than 3,000 patients in long-term clinical trials. ECL cell hyperplasia in those biopsies increased with time. No carcinoids or dysplasia were found. The label then adds the critical sentence: those studies were “of insufficient duration and size to rule out the possible influence of long-term administration”.

The structure of the argument is on the page. The drug raises gastrin. Gastrin drives ECL cell proliferation. ECL hyperplasia increased with time in the human studies. The human studies were not long enough or large enough to detect what comes next. The drug is approved for 4-8 weeks. Patients take it for years.

> ASK YOUR DOCTOR
> *The Prilosec label states that long-term human studies were of insufficient duration and size to rule out premalignant or malignant changes. What surveillance is being done in patients who have been on this drug for more than five years?*

The neurological signal

The Prilosec label section 13.1 describes a 52-week toxicity study in Sprague-Dawley rats. Brain astrocytomas — tumours of the glial cells that support neurons — were found in a small number of male rats receiving omeprazole at 0.4, 2, and 16 mg/kg/day, which the label notes is about 0.2 to 6.5 times the human dose on a body surface area basis. No astrocytomas were observed in female rats in this study. A 2-year follow-up study, the label states, did not find astrocytomas. The first finding is described and the second is offered as reassurance, but the original observation is not removed from the label.

The Prilosec post-marketing list under Nervous System/Psychiatric reads as a catalogue: depression, agitation, aggression, hallucinations, confusion, insomnia, nervousness, apathy, somnolence, anxiety, dream abnormalities, tremors, paraesthesia, vertigo. These are voluntary post-approval reports — the label cautions that frequency cannot be reliably estimated. The list is on the label because the reports came in.

The label does not discuss the dementia signal that has appeared in the post-2010 observational literature. The label predates the relevant studies. The patient prescribed the drug today is reading a document written before the relevant research existed, and is dependent on the prescriber to know the difference.

> ASK YOUR DOCTOR
> *The Prilosec post-marketing list includes confusion, hallucinations, depression and dream abnormalities. Is this drug being considered as a contributor in patients with new-onset cognitive or mood symptoms?*

The warnings added after approval

The Prilosec label was first approved in 1989. Over the following decades, the FDA added warnings for problems the original label did not mention. The dates appear on the labels themselves, under “Recent Major Changes”.

Clostridium difficile-associated diarrhoea was added to the Prilosec warnings in September 2012. The current label states that PPI therapy may be associated with an increased risk of C. difficile-associated diarrhoea, especially in hospitalised patients.

Bone fracture was added to the Nexium label in September 2010. The current Prilosec, Nexium and Protonix labels carry near-identical language: long-term and multiple daily dose PPI therapy may be associated with increased risk for osteoporosis-related fractures of the hip, wrist or spine, with the risk increased in patients on a year or longer of therapy. The labels then advise patients to use the lowest dose and shortest duration appropriate to

the condition.

Hypomagnesaemia was added to the Nexium label in June 2011. The text on all three PPI labels reports the same finding: low magnesium has occurred in patients on PPIs for at least three months, more often after a year, with serious consequences including tetany, arrhythmias and seizures. The label states that, in most affected patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of the PPI.

Cyanocobalamin (Vitamin B-12) deficiency appears as a dedicated warning, section 5.3, on the Protonix label. The label states that daily acid-suppressing therapy over a period longer than three years may lead to malabsorption of B-12 caused by hypo- or achlorhydria. The Prilosec label, in this version, does not carry a B-12 warning. The Nexium label lists vitamin B-12 deficiency in the post-marketing adverse reactions section but does not have a dedicated warning. Same molecule class. Same mechanism. Three different labels.

Interstitial nephritis appears in the post-marketing experience sections of all three PPI labels. The mechanism the labels describe is hypersensitivity, but the population affected is people taking the drug for years.

What links these warnings is when they appeared. The original 1989 label did not say PPIs increase the risk of broken bones, of bacterial diarrhoea that can kill, of seizures from low magnesium, of failure to absorb the vitamin needed for nerve function, or of inflammation in the kidneys. A generation of patients started the drug before any of these warnings existed.

> ASK YOUR DOCTOR
> *Were these warnings on the label when you first started prescribing this drug, or were they added afterward? If they were added, has my prescribed dose or duration been reviewed in light of them?*

What suppressing stomach acid actually does

Stomach acid is not a malfunction. The parietal cells produce hydrochloric acid at a pH around 1-2. At that pH, ingested protein denatures and becomes accessible to digestive enzymes. Iron is reduced from the ferric to the ferrous state, where it can be absorbed. Calcium is solubilised. Vitamin B-12 is liberated from food protein so it can be bound and transported. Most ingested bacteria are killed before they reach the small intestine.

The PPI labels describe what happens when this system is suppressed.

The Prilosec label, in section 12.2, states that omeprazole administered for 14 days in healthy subjects produced a significant increase in intragastric concentrations of viable bacteria. The pattern of bacterial species, the label adds, was unchanged from that commonly found

in saliva. Fourteen days of treatment changed which organisms could survive in the stomach. The label does not extend the observation to fourteen years.

Atrophic gastritis appears in section 5.2 of all three PPI labels. The Protonix language is representative: atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with the drug, particularly in patients who were H. pylori positive. The condition is the thinning and loss of the acid-producing tissue itself.

Fundic gland polyps appear in the Prilosec post-marketing list. The label notes that the polyps are benign and appear to be reversible when treatment is discontinued. Reversible — when the drug stops.

The downstream consequences track to acid suppression in each case. Bone fracture ties through calcium absorption, which depends on gastric acid to dissolve calcium salts. Hypomagnesaemia ties through the same pathway. B-12 deficiency ties through the failure to liberate B-12 from food protein. C. difficile ties through the loss of the acid barrier that normally kills ingested clostridia.

The labels do not assemble these findings into a single mechanism. Each appears in its own section, attributed to its own mechanism, with no language linking them. The mechanism that links them is the one the drug is designed to produce — sustained suppression of gastric acid in a system that depended on acid for functions the prescribing physician was not asked to consider.

> ASK YOUR DOCTOR
> *Given that gastric acid is required for absorption of B-12, calcium, magnesium and iron, and given that I have been taking a PPI for [duration], what testing has been done to check my levels of these nutrients?*

The patent extension nobody mentions

Prilosec (omeprazole) was approved in 1989. Its patent was scheduled to expire in 2001. AstraZeneca, the manufacturer, faced the loss of a multi-billion-dollar drug to generic competition.

In 2001, the FDA approved Nexium (esomeprazole). The Nexium label, on its first page, lists the initial US approval as 1989 and identifies the parent drug as omeprazole. Esomeprazole is the s-isomer of omeprazole. Omeprazole is sold as a racemic mixture — equal parts s-isomer and r-isomer. Nexium is the same molecule, with one half removed.

The Nexium label, in section 13.1, states that the carcinogenic potential of the drug was assessed using studies of omeprazole, of which esomeprazole is an enantiomer. The

reproductive toxicology section follows the same pattern: studies in rats and rabbits dosed with esomeprazole revealed no evidence of impaired fertility or harm to the fetus, while the omeprazole reproductive studies — referenced on the same page — produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions in rabbits.

The carcinogenicity data was carried over from the parent molecule. The reproductive toxicity data was carried over. The mechanism is the same. The new molecule was approved as a different drug, on the basis of being half of the old drug, with patent protection extending past 2001.

> ASK YOUR DOCTOR
> *Why was I prescribed Nexium specifically rather than omeprazole, given that the labels acknowledge they are isomers of the same drug and that the safety data is shared between them?*

Drug interactions: the mechanism is the indication

PPIs are designed to raise gastric pH. Many drugs depend on gastric acidity for their absorption. The PPI labels list these in the drug interactions section.

Atazanavir and nelfinavir — antiretroviral drugs used in HIV treatment. The Prilosec label states that co-administration is expected to substantially decrease atazanavir or nelfinavir plasma concentrations and may result in loss of therapeutic effect and the development of drug resistance. Co-administration is not recommended.

Ketoconazole, iron salts and digoxin — the labels note that PPIs may interfere with absorption of drugs where gastric pH is an important determinant of bioavailability. Digoxin toxicity is named explicitly: patients on PPIs and digoxin may need to be monitored. Iron salts are listed alongside without elaboration on the consequences of impaired iron absorption in patients taking the drug for years.

Warfarin — all three PPI labels note post-marketing reports of increased INR and prothrombin time in patients receiving PPIs and warfarin together. The labels add that increases in INR and prothrombin time may lead to abnormal bleeding and even death.

Methotrexate — added as a warning to the Prilosec label in January 2012 and to the Protonix label in May 2012. The labels state that PPIs may elevate and prolong serum levels of methotrexate and its metabolite, possibly leading to methotrexate toxicities. The recommended action: in high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered. The interaction was identified after years of co-prescription.

Clopidogrel — the Prilosec label section 5.5 warns of diminished anti-platelet activity of clopidogrel due to impaired CYP2C19 function by 80 mg omeprazole. Clopidogrel is prescribed to prevent blood clots in patients with cardiovascular disease. PPIs are commonly co-prescribed with clopidogrel because clopidogrel can cause stomach upset.

Tetrahydrocannabinol (THC) urine screens — Protonix label section 7.5 notes reports of false positive urine screening tests for THC in patients receiving PPIs. The label recommends an alternative confirmatory method. A patient on a PPI may fail a workplace drug screen for a substance they have not consumed.

> ASK YOUR DOCTOR
> *Of the medications I currently take, which depend on gastric pH for absorption or have known interactions with PPIs?*

Pregnancy, lactation and paediatric use

The Prilosec label, section 8.1, classifies omeprazole as Pregnancy Category C. The reasoning is on the same page. In pregnant rabbits, omeprazole at 5.5 to 56 times the human dose produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats at 5.6 to 56 times the human dose, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring. The label notes that post-marketing data in humans concluded therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk. The studies cited used first-trimester exposure, which is not when most drug effects on offspring manifest.

The lactation section of the Prilosec label states that omeprazole is excreted in human breast milk and that, because of the potential for tumorigenicity shown in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug. The Nexium and Protonix labels carry equivalent language. The carcinogenicity findings the labels describe in adult rats are the basis for advising mothers to choose between the drug and breastfeeding.

Prilosec, Nexium and Protonix are approved for paediatric use. Nexium is approved in children as young as one year for short-term GERD treatment. Prilosec is approved from age 1; the label states that safety and effectiveness in patients under 1 year of age have not been established. Protonix is approved at age 5 and above. The Prilosec label, in its paediatric clinical-trial section, notes that respiratory adverse reactions were the most frequently reported type in treated children, accounting for 75% of reported reactions in the 1-to-under-2 age group and 18.5% in the 2-to-16 group. Fever was the next most frequent in the youngest cohort, at 33%. The label adds that the safety and effectiveness of Prilosec for paediatric uses other than those already approved have not been established.

> ASK YOUR DOCTOR
> *Has the long-term effect of acid suppression in a developing child been studied? What is known about the consequences of inhibiting gastric acid during the years when bone density, gut microbial development and B-12 status are being established?*

The unique data on famotidine

Famotidine (Pepcid) is an H2 blocker, not a PPI. It blocks histamine receptors on parietal cells rather than the acid pump itself. It was approved in 1986 — three years before omeprazole — and dominated the acid-suppression market until PPIs displaced it. The Pepcid label is short. It is 16 pages compared to Prilosec's 45.

The Pepcid label does not warn for B-12 deficiency, fracture, hypomagnesaemia, atrophic gastritis or C. difficile. Its post-marketing list includes prolonged QT interval, hepatitis, agranulocytosis, anaphylaxis, rhabdomyolysis and toxic epidermal necrolysis. These are serious. They are also rare. The Pepcid label does not describe a class of long-term harms because famotidine does not produce 80-94% acid suppression. It produces partial suppression that the body can compensate around. The H2 receptor is one of several signals to the parietal cell. The H+/K+ ATPase is the only pump.

Famotidine is not the answer to the PPI trap. It is the comparison that shows the PPI label's harms are not inherent to acid suppression. They are inherent to near-total acid suppression, applied for longer than the indication contemplates.

> ASK YOUR DOCTOR
> *If acid suppression is appropriate for my condition, has an H2 blocker been considered as a less complete suppressor with a different long-term profile?*

What happens when patients try to stop

The PPI labels describe the trap by mechanism. The clinical experience of stopping is what patients actually face. The labels do not contain that experience because the labels describe drug action, not patient behaviour.

The Prilosec label states that secretory activity returns over 3 to 5 days, and that gastrin elevation persists for 1 to 2 weeks after discontinuation. The same label, describing fundic gland polyps, says they “appear to be reversible when treatment is discontinued”. For ECL cell hyperplasia, the Prilosec label points to a single rat study in which female animals were treated for one year and then followed for another year drug-free; no carcinoids were seen

at the end of that second year, and the difference between treated and control rats had narrowed. The label cites this as evidence of regression. It does not extend the finding to the human dosing pattern of years on, never off.

The Protonix label, in its 7-day discontinuation study, observed no rebound. The Nexium label notes that gastrin returned to baseline within four weeks after discontinuation. Four weeks is a long time to ride out resurgent heartburn.

The patient's window of return varies. The label data are from healthy volunteers and short courses. Patients on PPIs for a year or longer — the population in which the fracture and hypomagnesaemia warnings appeared — are not the population in which discontinuation studies were done. The drug is approved for 4-8 weeks. The discontinuation data are mostly for periods of similar length. Patients on the drug for years are running an experiment the label does not describe.

The standalone withdrawal essay in this series will go into what is known about coming off PPIs — tapering protocols, alternative approaches to the underlying conditions that produce reflux in the first place, and what the original symptom looks like once the drug response is separated from the rebound response. The labels themselves do not contain that information. They contain the mechanism of the trap, the carcinogenicity question the manufacturers admit is unresolved, the warnings added decade by decade as the harms became impossible to ignore, and the statement — printed on the prescribing information for one of the most prescribed drugs in the country — that efficacy beyond eight weeks has not been established. The labels are public. The patient on the drug has the same access to them as the prescriber.

Questions to take to your doctor

1. The Prilosec label states the drug is indicated for short-term treatment, with efficacy beyond 8 weeks “not established”. How long have I been on this drug, and what is the medical justification for continuing past the indicated duration?
2. The Protonix label states that pantoprazole was carcinogenic in long-term rodent studies, with the relevance to humans unknown. What surveillance, if any, is being done in long-term users to address this question?
3. If gastrin levels rise during PPI treatment and acid secretion is suppressed by 80-94%, what is the expected acid output during the days after I stop taking this drug?
4. The bone fracture, hypomagnesaemia and C. difficile warnings were added to PPI labels between 2010 and 2014. Were these warnings on the label when you first started prescribing this drug, and has my prescription been reviewed in light of them?

5. Given that gastric acid is required for absorption of B-12, calcium, magnesium and iron, what testing has been done to check my levels of these nutrients?
6. The Prilosec label notes that PPI therapy increases the bacterial concentrations in the stomach. What is known about long-term changes to my gut microbial population from sustained acid suppression?
7. Why was I prescribed this specific PPI rather than another, given that the labels indicate the safety findings are largely shared across the class?
8. Of the medications I currently take, which depend on gastric pH for absorption or have known interactions with PPIs?
9. If I am at risk for cardiovascular events and take clopidogrel, has the interaction with PPIs been considered in my prescription?
10. The Pepcid label is much shorter than the PPI labels and does not carry warnings for fracture, hypomagnesaemia or B-12 deficiency. If acid suppression is appropriate for my condition, has an H2 blocker been considered as an alternative?
11. What is the plan for tapering off this medication, and over what duration?
12. If I experience returning heartburn after stopping, how do I distinguish between the original condition reasserting itself and rebound acid hypersecretion produced by the drug?

> Disclaimer
> Nothing in this article is medical advice. Its purpose is to help readers read the documents that govern their own prescriptions and to ask better questions. The labels are public. They say what they say.

Sources

All citations are drawn from the FDA-approved prescribing information available at fda.gov/drugsatfda:

- PRILOSEC (omeprazole) — NDA 019810, AstraZeneca, revised 09/2012
- PROTONIX (pantoprazole sodium) — NDA 020987, Wyeth Pharmaceuticals, revised 05/2012
- NEXIUM (esomeprazole magnesium) — NDAs 021153, 021957, 022101, AstraZeneca, revised 06/2011
- PEPCID (famotidine) — NDA 019462, Valeant Pharmaceuticals, revised 06/2018