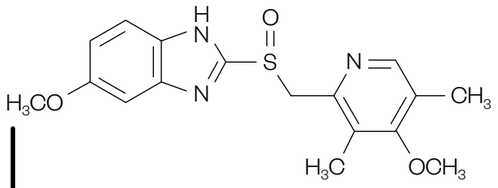
THE DEVELOPMENT AND SAFETY OF PROTON PUMP INHIBITORS

Since the discovery of omeprazole in 1979, dispensing of proton pump inhibitors (PPIs) in England has increased more than 100-fold, and several products are now available without prescription. Although PPIs are effective and generally well tolerated, observational studies suggest an association with several adverse effects. Further trials are needed to establish causal relationships.

DAWN CONNELLY



1979

Omeprazole, a PPI that blocks gastric hydrogen potassium ATPase and inhibits gastric acid secretion, is discovered by Swedish pharmaceutical company Astra Hässle. Human trials begin the following year.

Safety studies **Regulatory developments** **Prescription items dispensed in the community in England (millions)**

1985
Long-term rat carcinogenicity studies show development of slow-growing gastric tumours and human studies are suspended. But it is found that the tumours are caused by total inhibition of acid secretion and not related to omeprazole's safety, so human trials resume.

1988
Omeprazole launched as a prescription-only medicine in Europe for treatment of duodenal ulcer and other acid-related disorders. UK launch 1989 (Losec; Astra Hässle); US approval 1990 (Losec, later changed to Prilosec).

1990
Lansoprazole approved in France; claims to have greater bioavailability than omeprazole. UK launch 1994 (Zoton; Cyanamid); US approval 1995 (Prevacid; Takeda).

1992
Sentinel case-report identifies omeprazole as a possible cause of **acute interstitial nephritis**. First case reports for pantoprazole, lansoprazole and rabeprazole follow in 2004 and 2005.

1994
Pantoprazole launched in South Africa, Germany and UK (Protium; Altana Pharma); claims to have high bioavailability and a lower potential for drug interactions than other PPIs. US approval 1998 (Protonix; Takeda).

1997
Rabeprazole approved in Japan. European approval and UK launch (Pariet; Eisai) 1998. US approval 1999 (AcipHex; Eisai).

2000
Esomeprazole, an isomer of omeprazole, approved in Europe; claims to have superior acid-control to other PPIs and is first PPI licensed for use "on-demand". UK launch 2000 (Nexium; AstraZeneca); US approval 2001.

2003
Retrospective case-control study finds PPI use associated with increased risk of ***C. difficile* diarrhoea** (odds ratio [OR] 2.5, 95% confidence interval [CI] 1.5–4.2) (*J Hosp Infect* 2003;54:243). Further observational studies in 2005, 2010, 2011 and 2015 confirm the link (*JAMA* 2005;294:2989, *Arch Intern Med* 2010;170:772, *N Engl J Med* 2011;365:1693, *JAMA Intern Med* 2015;175:784).

2003
Omeprazole reclassified from a prescription-only to pharmacy medicine in UK; over-the-counter product (Zanprol; GlaxoSmithKline) launched in 2004 for relief of reflux-like symptoms.

2004
Population-based cohort study finds current use of PPIs is associated with increased risk of **community-acquired pneumonia** (adjusted relative risk 1.89, 95% CI 1.36–2.62) (*JAMA* 2004;292:1955). Observational studies in 2007 and 2008 confirm the link, especially when PPIs have been recently started (OR 5.0, 95% CI 2.1–11.7) (*Arch Intern Med* 2007;167:950 and *Ann Intern Med* 2008;149:391).

2006
Hypomagnesemia reported as potential side effect of PPIs. The US Food and Drug Administration (FDA) warns in 2011 that long-term PPI use is linked with low magnesium and associated risk for cardiac arrhythmias, but little risk with short courses. In 2015, systematic review of observational studies suggests PPI use for >2 years associated with increased risk of **vitamin B12 deficiency** (HR 1.83, 95% CI 1.36–2.46) (*Intern Med J* 2015;45:409).

2006
Observational study reports that long-term, high-dose PPIs in people aged >50 years is associated with increased risk of hip fracture (adjusted OR 2.65, 95% CI, 1.80–3.90) (*JAMA* 2006;296:2947). Further study in 2008 confirms link and finds short-term use does not increase risk (*CMAJ* 2008;179:319). In 2010, the FDA warns of possible increased risk of hip, wrist and spine fractures with PPIs.

2009
Large observational study reports concomitant use of clopidogrel and PPIs in people aged >65 years may increase risk of death from recurrent **heart attack** (adjusted OR 1.27, 95% CI 1.03–1.57) (*CMAJ* 2009;180:713). In 2010, a double-blind randomised controlled trial does not show any significant increase in risk of cardiovascular events (*N Engl J Med* 2010;363:1909). However, in 2012, the FDA advises that concomitant use of esomeprazole and omeprazole with clopidogrel should be avoided because it reduces the pharmacological activity of clopidogrel.

2009
US approval **dexlansoprazole** (Kapidex, later changed to Dexilant; Takeda); dual-delayed release formulation that relieves GERD for up to 24 hours. Approved in 16 EU countries 2013; not yet launched in UK.

2009
Pantoprazole reclassified in Europe and can be sold in pharmacies for short-term treatment of reflux. Launched as over-the-counter product in UK pharmacies 2010 (Pantoloc Control; GSK).

2012
Rabeprazole reclassified in Europe and can be sold in pharmacies for short-term relief of reflux. Pariet Pharmacy (Eisai) never launched in UK.

2013
Observational study finds patients with **renal disease** nearly twice as likely to have been exposed to PPIs than those without it (OR 1.72, 95% CI 1.27–2.32) (*BMC Nephrology* 2013;14:150). Two studies in 2016 confirm the link (*JAMA Intern Med* 2016;176:238 and *JASN*; online, 14 April 2016).

2013
Esomeprazole reclassified as pharmacy medicine in Europe for short-term treatment of reflux; never launched in the UK. Becomes first PPI to be sold outside of pharmacies in UK (Nexium Control; Pfizer) after further reclassification in 2015.

2016
Observational cohort study suggests PPI use in people aged >75 years is associated with increased risk of **dementia** (HR 1.44, 95% CI 1.36–1.52) (*JAMA Neurol* 2016;73:410).

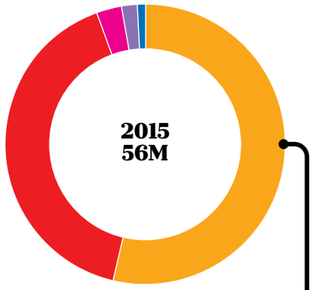
2016
Preclinical study finds PPIs can cause premature ageing of blood vessel endothelial cells, providing a possible explanation for link between PPIs and increased risk for **heart attack**, **renal failure** and **dementia** (*Circ Res*; online, 10 May 2016).

1985 1990 1995 2000 2005 2010 2015

60M 50M 40M 30M 20M 10M 0

OMEPRAZOLE MOST WIDELY PRESCRIBED

Omeprazole was the most commonly dispensed PPI in the community in England in 2015, and the second most commonly dispensed medicine overall (simvastatin came first with 34.4m items).



30.1M Omeprazole
22.9M Lansoprazole
1.5M Esomeprazole
1.1M Pantoprazole
0.4M Rabeprazole

Graphics: Alisdair Macdonald; **Sources:** Health and Social Care Information Centre, Medicines and Healthcare products Regulatory Agency, Proprietary Association of Great Britain, US Food and Drug Administration, Takeda, Eisai. **Editorial advisers:** Emily McDonald, McGill University Health Center, Montréal; Sarah Cripps, Oxford University Hospitals NHS Trust.