Omeprazole *(BAN, USAN, rINN)*

H-168/68; Omepratsoli; Omeprazol; Omeprazolas; Oméprazole; Omeprazolum. (*RS*)-5-Methoxy-2-(4-methoxy-3,5-dimethyl-2-pyridylmethylsulphinyl)benzimidazole.

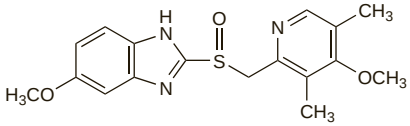
Омепразол

$C_{17}H_{19}N_3O_3S$ = 345.4.

CAS — 73590-58-6.

ATC — A02BC01.

ATC Vet — QA02BC01.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Omeprazole). A white or almost white powder. It exhibits polymorphism. Very slightly soluble in water; sparingly soluble in alcohol and in methyl alcohol; soluble in dichloromethane. It dissolves in dilute solutions of alkali hydroxides. Store in airtight containers at a temperature between 2° and 8°. Protect from light.

USP 31 (Omeprazole). A white to off-white powder. Very slightly soluble in water; sparingly soluble in alcohol and in methyl alcohol; soluble in dichloromethane. Store in airtight containers at a temperature not exceeding 8°. Protect from moisture.

Omeprazole Magnesium *(BANM, USAN, rINNM)*

Magnesii Omeprazolum; Omeprazol magnésico; Oméprazole magnésique; Oméprazole Magnesique; Omeprazolum magnesicum.

Магния Омепразол

$C_{34}H_{36}MgN_6O_6S_2$ = 713.1.

CAS — 95382-33-5.

ATC — A02BC01.

ATC Vet — QA02BC01.

Pharmacopoeias. In *US.*

USP 31 (Omeprazole Magnesium). A white to off-white powder. Very soluble in water and in dichloromethane; slightly soluble in alcohol; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Omeprazole Sodium *(BANM, USAN, rINNM)*

Natrii Omeprazolum; Omepratsolinatrium; Omeprazol sódico; Omeprazol sodná sůl monohydrát; Oméprazole sodique; Omeprazolnatrium; Omeprazol-nátrium; Omeprazolo natrio druska; Omeprazolum natricum; Omeprazolum Natricum Monohydricum.

Натрий Омепразол

$C_{17}H_{18}N_3NaO_3S$ = 367.4.

CAS — 95510-70-6.

ATC — A02BC01.

ATC Vet — QA02BC01.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Omeprazole Sodium). A white or almost white, hygroscopic powder. Freely soluble in water and in alcohol; very slightly soluble in dichloromethane; soluble in propylene glycol. The pH of a 2% solution in water is 10.3 to 11.3. Store in airtight containers. Protect from light.

Adverse Effects

Proton pump inhibitors are generally well tolerated, and adverse effects are relatively infrequent. The adverse effects reported most often with omeprazole and other proton pump inhibitors have been headache, diarrhoea, and skin rashes; they have sometimes been severe enough to require stopping treatment. Other effects include pruritus, dizziness, fatigue, constipation, nausea and vomiting, flatulence, abdominal pain, arthralgia and myalgia, urticaria, and dry mouth. Isolated cases of photosensitivity, bullous eruption, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have occurred. Hypersensitivity reactions, including fever, bronchospasm, angioedema, and anaphylaxis have been reported. Effects on the CNS include occasional insomnia, somnolence, and vertigo; reversible confusional states, agitation, depression, and hallucinations have occurred in severely ill patients. Raised liver enzymes, and isolated cases of hepatitis, jaundice, hepatic failure, and hepatic encephalopathy, have been reported. Other adverse effects reported rarely include paraesthesia, blurred vision, alopecia, stomatitis, increased sweating, taste disturbances, peripheral oedema, malaise, hyponatraemia, blood disorders (including agranulocytosis, leucopenia, and thrombocytopenia), gynaecomastia, impotence, and interstitial nephritis.

Proton pump inhibitors may increase the risk of gastrointestinal infections because of their acid suppressive effects.

Early toxicological studies identified carcinoid-like tumours of the gastric mucosa in *rats* given very high doses of omeprazole over long periods; this is reviewed in more detail under Gastrointestinal Tumours, below.

Incidence of adverse effects. Prescription-event monitoring for 16 205 patients prescribed omeprazole, 17 329 prescribed lansoprazole, and 11 541 prescribed pantoprazole indicated that adverse events were reported infrequently, with the most common being gastrointestinal disturbances and headache. The incidences of diarrhoea, the most commonly reported event, per 1000 days of exposure, were 0.18 for omeprazole, 0.39 for lansoprazole, and 0.23 for pantoprazole. Despite the inherent biases of such a cohort study, there did seem to be some evidence that lansoprazole might be associated with a somewhat greater risk of diarrhoea, particularly in the elderly.[1]

1. Martin RM, *et al.* The rates of common adverse events reported during treatment with proton pump inhibitors used in general practice in England: cohort studies. *Br J Clin Pharmacol* 2000; **50:** 366–72.

Effects on the blood. There have been rare cases of leucopenia, agranulocytosis, thrombocytopenia, and pancytopenia, with omeprazole and other proton pump inhibitors such as lansoprazole and pantoprazole.[1-3] Auto-immune haemolytic anaemia has also been reported with omeprazole.[4]

1. Holt TL, *et al.* Neutropenia associated with omeprazole. *Med J Aust* 1999; **170:** 141–2.
2. Zlabek JA, Anderson CG. Lansoprazole-induced thrombocytopenia. *Ann Pharmacother* 2002; **36:** 809–11.
3. Watson TD, *et al.* Pantoprazole-induced thrombocytopenia. *Ann Pharmacother* 2006; **40:** 758–61.
4. Butt MI, *et al.* Autoimmune haemolytic anaemia associated with use of omeprazole. *Br J Hosp Med* 2007; **68:** 108.

Effects on the cardiovascular system. Results and preliminary analyses from 2 studies raised concerns about a possible increased risk of myocardial infarction, cardiac failure, and cardiac-related sudden death in patients taking *omeprazole* or *esomeprazole* compared with patients who received surgery for gastro-oesophageal reflux disease.[1,2] However, an FDA safety review found that patients who underwent surgery tended to be younger and less likely to have a history of cardiac problems or cardiac risk factors than those treated with one of the drugs.[2] The FDA concluded that long-term use of these drugs is not likely to be associated with an increased risk of cardiac problems.[3] However, while Health Canada[4] considered that there was no evidence to support such an increased risk with long-term use of esomeprazole they were unable to make such a definitive conclusion for omeprazole.

1. FDA. Early communication about an ongoing safety review: omeprazole (Prilosec) esomeprazole (Nexium) (issued 9th August 2007). Available at: http://www.fda.gov/cder/drug/early_comm/omeprazole_esomeprazole.htm (accessed 28/01/08)
2. FDA. Follow-up to the August 9, 2007, communication about the ongoing safety review of omeprazole and esomeprazole (issued 10th December 2007). Available at: http://www.fda.gov/cder/drug/early_comm/omeprazole_esomepazole_update.htm (accessed 28/01/08)
3. FDA. FDA's safety reviews of Prilosec and Nexium find no evidence of increased rates of cardiac events (issued 10th December 2007). Available at: http://www.fda.gov/bbs/topics/NEWS/2007/NEW01754.html (accessed 28/01/08)
4. Health Canada. Health Canada completes safety review of Losec (omeprazole) and Nexium (esomeprazole) (issued 27 February 2008). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_34-eng.php (accessed 09/07/08)

Effects on the endocrine system. Up to December 1991, WHO had received 30 reports of impotence or gynaecomastia which might have been due to omeprazole;[1] of these reports 15 were of impotence, 13 of gynaecomastia in men, and 2 of breast enlargement in women. The Spanish Pharmacovigilance System reported 24 cases of gynaecomastia in association with use of proton pump inhibitors, including lansoprazole and rabeprazole, between January 1982 and July 2006. In most of the cases, gynaecomastia improved after stopping the drug.[2] For reference to a case-control study showing no statistical link between gynaecomastia and omeprazole, see under Cimetidine, p.1717.

1. Lindquist M, Edwards IR. Endocrine adverse effects of omeprazole. *BMJ* 1992; **305:** 451–2.
2. Carvajal A, *et al.* Gynaecomastia associated with proton pump inhibitors: a case series from the Spanish Pharmacovigilance System. *Drug Safety* 2007; **30:** 527–31.

Effects on the eyes. Visual disturbances associated with the use of omeprazole have included 6 cases of irreversible blindness or visual impairment in severely ill patients given the drug intravenously, and 13 cases of visual disturbances associated with oral use.[1] As a result of concern about these effects the availability of intravenous omeprazole was restricted in Germany; however, the consensus appears to be that a causal link has not been established between omeprazole and these ocular effects. Suggestions that visual (and also auditory[2]) impairment could follow drug-induced vasculitis[2-4] appear to be contentious.[1,5-7] A cohort study involving 140 128 patients receiving antisecretory therapy, 33 988 of whom received omeprazole, found no evidence that any of the drugs used was associated with a major increase in risk of vascular or inflammatory disorders of the eye;[8] however, the statistical power of this study was not high.[9]

1. Creutzfeldt WC, Blum AL. Safety of omeprazole. *Lancet* 1994; **343:** 1098.
2. Schönhöfer PS. Intravenous omeprazole and blindness. *Lancet* 1994; **343:** 665.
3. Schönhöfer PS. Safety of omeprazole and lansoprazole. *Lancet* 1994; **343:** 1369–70.
4. Schönhöfer PS, *et al.* Ocular damage associated with proton pump inhibitors. *BMJ* 1997; **314:** 1805.
5. Colin-Jones D. Safety of omeprazole and lansoprazole. *Lancet* 1994; **343:** 1369.
6. Lessell S. Omeprazole and ocular damage. *BMJ* 1998; **316:** 67.
7. Sachs G. Omeprazole and ocular damage. *BMJ* 1998; **316:** 67–8.
8. García Rodríguez LA, *et al.* A cohort study of the ocular safety of anti-ulcer drugs. *Br J Clin Pharmacol* 1996; **42:** 213–16.
9. Merlo J, Ranstam J. Ocular safety of anti-ulcer drugs. *Br J Clin Pharmacol* 1997; **43:** 449.

Effects on the kidneys. Acute interstitial nephritis developed in 2 elderly patients given *omeprazole* for the treatment of gastro-oesophageal reflux disease.[1,2] When the drug was stopped, renal function improved rapidly in 1 patient, but recurred upon rechallenge,[1] while in the other renal function remained severely affected for several months.[2] It was postulated that this adverse effect might have an allergic mechanism.[2] In these cases interstitial nephritis was associated with rash and eosinophilia; however, a further 2 cases of acute interstitial nephritis associated with omeprazole therapy in elderly patients[3,4] did not exhibit these symptoms. In another report, associated rash without eosinophiluria was seen.[5]

The Australian Adverse Drug Reactions Advisory Committee (ADRAC)[6] stated in April 2003 that it had received 18 biopsy-confirmed reports of interstitial nephritis associated with the use of omeprazole. These patients had presented with symptoms including weight loss, malaise, fever, and nausea; polyuria and polydipsia occurred in one case. Most patients had raised plasma-urea and/or plasma-creatinine concentrations. ADRAC had also received 2 reports of interstitial nephritis associated with *rabeprazole*.[6] A case report (in March 2005) of 2 cases of interstitial nephritis associated with the omeprazole isomer *esomeprazole* noted that, by October 2004, the manufacturer had reported being aware of some 15 cases worldwide possibly associated with the drug, and at least 200 associated with omeprazole.[7] Acute interstitial nephritis has also been associated with the use of *pantoprazole* in an elderly woman for the treatment of gastro-oesophageal reflux disease.[8]

1. Ruffenach SJ, *et al.* Acute interstitial nephritis due to omeprazole. *Am J Med* 1992; **93:** 472–3.
2. Christensen PB, *et al.* Renal failure after omeprazole. *Lancet* 1993; **341:** 55.
3. Assouad M, *et al.* Recurrent acute interstitial nephritis on rechallenge with omeprazole. *Lancet* 1994; **344:** 549.
4. Jones B, *et al.* Acute interstitial nephritis due to omeprazole. *Lancet* 1994; **344:** 1017–18.
5. Kuiper JJ. Omeprazole-induced acute interstitial nephritis. *Am J Med* 1993; **95:** 248.
6. Adverse Drug Reactions Advisory Committee (ADRAC). Interstitial nephritis with the proton pump inhibitors. *Aust Adverse Drug React Bull* 2003; **22:** 3. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0304.htm (accessed 07/05/04)
7. Geevasinga N, *et al.* Acute interstitial nephritis secondary to esomeprazole. *Med J Aust* 2005; **182:** 235–6.
8. Ra A, Tobe SW. Acute interstitial nephritis due to pantoprazole. *Ann Pharmacother* 2004; **38:** 41–5.

Effects on the liver. Raised liver enzymes have occurred with omeprazole and other proton pump inhibitors, and there have been isolated cases of hepatotoxicity. For a study suggesting a relatively low incidence of acute liver injury in patients receiving omeprazole see Cimetidine, p.1717.

References.

1. Jochem V, *et al.* Fulminant hepatic failure related to omeprazole. *Am J Gastroenterol* 1992; **87:** 523–5.
2. Kourg SI, *et al.* Omeprazole and the development of acute hepatitis. *Eur J Emerg Med* 1998; **5:** 467–9.

Effects on the musculoskeletal system. Progressive muscular weakness suggestive of *myopathy* developed in a 78-year-old patient given oral omeprazole.[1] After 4 weeks of treatment the patient required assistance in walking and rising from squatting. Weakness resolved on withdrawal of the drug, but returned on rechallenge. Acute myopathy has also been reported after a single infusion of omeprazole.[2] Analysis of the WHO adverse drug reaction database in March 2005 revealed 868 reports associating proton pump inhibitors with *myalgia*, of which 292 cases had symptoms indicative of muscle disorders including *polymyositis* and *rhabdomyolysis*.[3] Reports implicated omeprazole, pantoprazole, lansoprazole, esomeprazole, and rabeprazole, and it was suggested that myopathy was probably a class effect. The mechanism might involve induction of auto-immune antibodies.

A report of 5 cases of *arthralgia*, sometimes associated with swelling of the affected joints, in patients receiving omeprazole,[4] also noted that some reported cases of omeprazole-associated headache were accompanied by arthralgia or myalgia. In another case[5] arthralgia in a patient with a hereditary myopathy receiving

omeprazole appeared to represent one aspect of a drug-induced *lupus* syndrome, being accompanied by malaise, fever, Raynaud's phenomenon, raised antinuclear antibody titres, and anticardiolipin and antihistone antibodies. Symptoms resolved on withdrawal of the drug.

A case of *eosinophilia* and myalgia related to lansoprazole treatment has been reported.[6]

There has also been a report of 2 cases of acute *gout* associated with omeprazole;[7] in one patient symptoms, which resolved on withdrawal, recurred on rechallenge. However, case control studies have failed to show an increased risk of polyarthralgia[8] or gout[9] associated with omeprazole use.

A large case-control study found an increased risk of *hip fracture* with more than 1 year of proton pump inhibitor therapy, especially with those patients on high doses.[10] The authors theorised that calcium malabsorption secondary to acid suppression may explain this association. While further studies were deemed necessary to confirm these findings, they suggested that calcium intake be emphasised in elderly patients taking proton pump inhibitors.

1. Garrote FJ, *et al.* Subacute myopathy during omeprazole therapy. *Lancet* 1992; **340:** 672.
2. Tuccori M, *et al.* Acute severe myopathy following a single infusion of omeprazole. *Ann Pharmacother* 2006; **40:** 352–3.
3. Clark DWJ, Strandell J. Myopathy including polymyositis: a likely class adverse effect of proton pump inhibitors? *Eur J Clin Pharmacol* 2006; **62:** 473–9.
4. Beutler M, *et al.* Arthralgias and omeprazole. *BMJ* 1994; **309:** 1620.
5. Sivakumar K, Dalakas MC. Autoimmune syndrome induced by omeprazole. *Lancet* 1994; **344:** 619–20.
6. Smith JD, *et al.* Possible lansoprazole-induced eosinophilic syndrome. *Ann Pharmacother* 1998; **32:** 196–200.
7. Kraus A, Flores-Suárez LF. Acute gout associated with omeprazole. *Lancet* 1995; **345:** 461–2.
8. Meier CR, Jick H. Omeprazole, H blockers, and polyarthralgia: case-control study. *BMJ* 1997; **315:** 1283.
9. Meier CR, Jick H. Omeprazole, other antiulcer drugs and newly diagnosed gout. *Br J Clin Pharmacol* 1997; **44:** 175–8.
10. Yang Y-X, *et al.* Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA* 2006; **296:** 2947–53. Correction. *ibid.* 2007; **297:** 470.

Effects on the nervous system. Ataxia has been reported in a patient given omeprazole;[1] symptoms resolved on stopping the drug. A patient given rabeprazole developed marked anxiety with panic attacks, episodic night terrors, confusion, and attention deficit.[2] Her symptoms resolved 2 days after stopping therapy. A month later, she was given esomeprazole, with no adverse neuropsychiatric symptoms. The authors hypothesised that rabeprazole use had resulted in significantly greater plasma gastrin concentrations than esomeprazole, which may have affected gastrin receptors in the brain.

1. Varona L, *et al.* Gait ataxia during omeprazole therapy. *Ann Pharmacother* 1996; **30:** 192.
2. Polimeni G, *et al.* Rabeprazole and psychiatric symptoms. *Ann Pharmacother* 2007; **41:** 1315–17.

Effects on the respiratory system. An intractable, dry, nonproductive cough started abruptly in a 42-year-old non-smoker given omeprazole for gastro-oesophageal reflux disease (GORD). The cough was initially thought to be related to the GORD and treatment was continued for 4 months, without any cessation in the cough. Omeprazole was stopped, and the cough ceased abruptly, with no recurrence during a 2-year follow-up.[1]

1. Howaizi M, Delafosse C. Omeprazole-induced intractable cough. *Ann Pharmacother* 2003; **37:** 1607–9.

Effects on the skin. An extensive blistering erythematous skin rash in an elderly woman given omeprazole[1] was characteristic of acute disseminated epidermal necrosis. The UK CSM had received 223 reports of cutaneous reactions to omeprazole up to August 1992, including 6 of erythema multiforme, but none of this severity. Other severe reactions that have subsequently been reported include a toxic bullous skin reaction,[2] exfoliative dermatitis,[3,4] erythema multiforme,[4] toxic erythema,[4] and dermatomyositis.[5] One patient developed exfoliative dermatitis with both omeprazole and lansoprazole.[4] The authors of this report noted that by January 1998 a total of 1296 skin reactions to omeprazole, 500 to lansoprazole, and 44 to pantoprazole, had been reported to the CSM. Most were non-specific rashes, pruritus, urticaria, erythematous rashes, and photosensitive eruptions. A lichenoid reaction that occurred in a patient taking omeprazole cleared after ceasing the drug, but recurred during treatment with both lansoprazole and pantoprazole.[6] Proton pump inhibitors, including esomeprazole, have been reported to worsen vitiligo.[7]

For a report of urticaria and angioedema possibly associated with the formulation of omeprazole see Hypersensitivity, below. For the association of rash with interstitial nephritis, see Effects on the Kidneys, above.

1. Cox NH. Acute disseminated epidermal necrosis due to omeprazole. *Lancet* 1992; **340:** 857.
2. Stenier C, *et al.* Bullous skin reaction induced by omeprazole. *Br J Dermatol* 1995; **133:** 343–4.
3. Epelde Gonzalo FD, *et al.* Exfoliative dermatitis related to omeprazole. *Ann Pharmacother* 1995; **29:** 82–3.
4. Cockayne SE, *et al.* Severe erythrodermic reactions to the proton pump inhibitors omeprazole and lansoprazole. *Br J Dermatol* 1999; **141:** 173–5.
5. Pan Y, *et al.* Omeprazole-induced dermatomyositis. *Br J Dermatol* 2006; **154:** 557–8.
6. Bong JL, *et al.* Lichenoid drug eruption with proton pump inhibitors. *BMJ* 2000; **320:** 283.
7. Schallreuter KU, Rokos H. From the bench to the bedside: proton pump inhibitors can worsen vitiligo. *Br J Dermatol* 2007; **156:** 1371–3.

Fever. Fever, associated with severe myalgia and headache, was seen in a 64-year-old man on 2 occasions, several hours after taking a dose of esomeprazole.[1] Although it was suggested[2] that the patient's hyperpyrexia was due to a hypersensitivity reaction, the authors argued[3] that esomeprazole may have interfered with the hypothalamic regulatory centres of body temperature.[1,3]

1. Grattagliano I, *et al.* Esomeprazole-induced central fever with severe myalgia. *Ann Pharmacother* 2005; **39:** 757–60.
2. Su SS, *et al.* Comment: esomeprazole-induced central fever with severe myalgia. *Ann Pharmacother* 2005; **39:** 1764.
3. Grattagliano I. Comment: esomeprazole-induced central fever with severe myalgia. *Ann Pharmacother* 2005; **39:** 1765.

Gastrointestinal tumours. Early toxicological studies in *rats* given high doses of omeprazole over 2 years identified carcinoid tumours of the gastric mucosa associated with complete block of gastric acid secretion leading to *hypergastrinaemia and hyperplasia of enterochromaffin-like cells*.[1] This has been the main issue concerning the safety of omeprazole and other proton pump inhibitors and initially led to restrictions in use and duration of treatment. A drug manufacturer, *Glaxo*, developed a new test to detect genotoxicity of antisecretory drugs which indicated that a genotoxic effect of omeprazole could not be discounted.[2] This study was heavily criticised; more established genotoxicity tests have been reported to be negative for omeprazole,[3-5] and other groups have not been able to replicate the findings with the new test.[6] The lowest doses at which *Glaxo* found[2] a genotoxic effect of omeprazole were 10 to 20 mg/kg and the clinical significance of their results was questioned.[3] Long-term studies of omeprazole in patients with Zollinger-Ellison syndrome have found no increase in fasting serum-gastrin concentrations and no evidence of gastric carcinoid tumours.[7,8] For mention of the risk of proton pump inhibitors delaying the diagnosis of gastric carcinoma, see under Precautions, below. Hypergastrinaemia can occur with both short- and long-term omeprazole therapy,[9] and may be higher in patients with *Helicobacter pylori* infection.[10,11] Patients who had *H. pylori* eradicated before long-term omeprazole treatment had lower gastrin concentrations than those who did not, since *H. pylori* eradication reduced the pretreatment gastrin concentrations.[12]

H. pylori is also a cause of *atrophic gastritis*, another risk factor for stomach cancer, and one study found that omeprazole increased the risk of atrophic gastritis in *H. pylori*-positive patients with gastro-oesophageal reflux disease.[13] However, the results of this study require confirmation since it was nonrandomised and retrospective. Nevertheless, some have suggested that it may be appropriate to eradicate *H. pylori* before long-term treatment with a proton pump inhibitor.[12,13] Conversely, there is some evidence that *H. pylori* may be protective in gastro-oesophageal reflux disease.[14]

There has been a report of *gastric polyps* developing in 3 of 8 patients after receiving omeprazole 20 or 40 mg daily for one year.[15] In a subsequent report it was noted that these omeprazole-induced fundic gland polyps had remained asymptomatic and non-malignant for up to five years after their onset.[16]

Further long-term studies of omeprazole may be needed before a realistic risk assessment can be made.

1. Ekman L, *et al.* Toxicological studies on omeprazole. *Scand J Gastroenterol* 1985; **20** (suppl 108): 53–69.
2. Burlinson B, *et al.* Genotoxicity studies of gastric acid inhibiting drugs. *Lancet* 1990; **335:** 419.
3. Ekman L, *et al.* Genotoxicity studies of gastric acid inhibiting drugs. *Lancet* 1990; **335:** 419–20.
4. Wright NA, Goodlad RA. Omeprazole and genotoxicity. *Lancet* 1990; **335:** 909–10.
5. Helander HF, *et al.* Omeprazole and genotoxicity. *Lancet* 1990; **335:** 910–11.
6. Goodlad RA. Acid suppression and claims of genotoxicity: what have we learned? *Drug Safety* 1994; **10:** 413–19.
7. Lloyd-Davies KA, *et al.* Omeprazole in the treatment of Zollinger-Ellison syndrome: a 4-year international study. *Aliment Pharmacol Ther* 1988; **2:** 13–32.
8. Maton PN, *et al.* Long-term efficacy and safety of omeprazole in patients with Zollinger-Ellison syndrome: a prospective study. *Gastroenterology* 1989; **97:** 827–36.
9. Koop H, *et al.* Serum gastrin levels during long-term omeprazole treatment. *Aliment Pharmacol Ther* 1990; **4:** 131–8.
10. Sanduleanu S, *et al.* Serum gastrin and chromogranin A during medium- and long-term acid suppressive therapy: a case-control study. *Aliment Pharmacol Ther* 1999; **13:** 145–53.
11. Kuipers EJ. Proton pump inhibitors and gastric neoplasia. *Gut* 2006; **55:** 1217–21.
12. El-Nujumi A, *et al.* Eradicating Helicobacter pylori reduces hypergastrinaemia during long term omeprazole treatment. *Gut* 1998; **42:** 159–65.
13. Kuipers EJ, *et al.* Atrophic gastritis and Helicobacter pylori infection in patients with reflux esophagitis treated with omeprazole or fundoplication. *N Engl J Med* 1996; **334:** 1018–22.
14. Labenz J, Malfertheiner P. Helicobacter pylori in gastro-oesophageal reflux disease: causal agent, independent or protective factor? *Gut* 1997; **41:** 277–80.
15. Graham JR. Gastric polyposis: onset during long-term therapy with omeprazole. *Med J Aust* 1992; **157:** 287–8.
16. Graham JR. Gastric acne: omeprazole-induced fundic gland polyposis. *Med J Aust* 1998; **168:** 93.

Hypersensitivity. Cases of anaphylactic reactions after treatment with omeprazole, lansoprazole, and pantoprazole, have been reported in the literature and to WHO.[1]

Urticaria, facial angioedema, and bronchospasm in a patient given omeprazole capsules did not recur when the patient was given omeprazole granules and the reaction might have been precipitated by the ingredients of the capsule shell.[2]

See also under Effects on the Kidney, and Effects on the Musculoskeletal System, above.

1. Natsch S, *et al.* Anaphylactic reactions to proton-pump inhibitors. *Ann Pharmacother* 2000; **34:** 474–6.
2. Haeney MR. Angio-oedema and urticaria associated with omeprazole. *BMJ* 1992; **305:** 870.

Infection. Oesophageal candidiasis occurred in 2 elderly patients given omeprazole but was successfully treated with antifungal therapy. It was postulated that gastric acid secretion and a degree of physiological reflux of acid into the oesophagus might normally play a protective role in preventing candidal infection.[1] A case-control study found that yeast was recovered more often from peritoneal cultures in those patients with community-acquired peritonitis who had previously used proton pump inhibitors, although the trend was non-significant.[2] The profound reduction in acid secretion produced by omeprazole may also predispose to gastrointestinal infection;[3] there is some evidence for an increased risk of community-acquired pneumonia,[3] and campylobacter infection,[4] as well as a report of recurrent salmonellal infection.[5] Data from cohort and case-control studies[6-8] suggest that gastric acid suppression by proton pump inhibitors may also be a risk factor for *Clostridium difficile*-associated diarrhoea. For evidence of an increased risk of pneumonia in primary-care patients prescribed proton pump inhibitors see p.1717.

1. Larner AJ, Lendrum R. Oesophageal candidiasis after omeprazole therapy. *Gut* 1992; **33:** 860–1.
2. Cat TB, *et al.* Potential influence of antisecretory therapy on the development of Candida-associated intraabdominal infection. *Ann Pharmacother* 2008; **42:** 185–91.
3. Canani RB, *et al.* Working Group on Intestinal Infections of the Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP). Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. *Pediatrics* 2006; **117:** e817–e820.
4. Neal KR, *et al.* Omeprazole as a risk factor for campylobacter gastroenteritis: case-control study. *BMJ* 1996; **312:** 414–15.
5. Wingate DL. Acid reduction and recurrent enteritis. *Lancet* 1990; **335:** 222.
6. Cunningham R, *et al.* Proton pump inhibitors as a risk factor for Clostridium difficile diarrhoea. *J Hosp Infect* 2003; **54:** 243–5.
7. Dial S, *et al.* Risk of Clostridium difficile diarrhea among hospital inpatients prescribed proton pump inhibitors: cohort and case-control studies. *Can Med Assoc J* 2004; **171:** 33–8.
8. Dial S, *et al.* Use of gastric acid–suppressive agents and the risk of community-acquired Clostridium difficile-associated disease. *JAMA* 2005; **294:** 2989–95.

Lupus syndrome. For a report of drug-induced lupus syndrome associated with omeprazole therapy, see Effects on the Musculoskeletal System, above.

Malabsorption. Omeprazole has been reported to result in a substantial reduction in *cyanocobalamin* (vitamin B_{12}) absorption,[1] probably related to the increase in gastric pH, and indicating a potential risk of vitamin deficiency with long-term therapy.[2] UK licensed product information recommends that severely ill children, who may have borderline body stores of cyanocobalamin, should have serum vitamin B_{12} concentrations monitored if they require long-term therapy. Omeprazole has also been reported to impair the bioavailability of dietary *vitamin C*.[3] *Fat* malabsorption, secondary to increased deconjugation of bile acids caused by bacterial overgrowth in the jejunum, has also been reported with omeprazole treatment.[4] For the suggestion that proton pump inhibitors can cause *calcium* malabsorption, see Effects on the Musculoskeletal System, above.

1. Marcuard SP, *et al.* Omeprazole therapy causes malabsorption of cyanocobalamin (vitamin B). *Ann Intern Med* 1994; **120:** 211–15.
2. Termanini B, *et al.* Effect of long-term gastric acid suppressive therapy on serum vitamin B levels in patients with Zollinger-Ellison syndrome. *Am J Med* 1998; **104:** 422–30.
3. Henry EB, *et al.* Proton pump inhibitors reduce the bioavailability of dietary vitamin C. *Aliment Pharmacol Ther* 2005; **22:** 539–45.
4. Shindo K, *et al.* Omeprazole induces altered bile acid metabolism. *Gut* 1998; **42:** 266–71.

Overdosage. A report of 2 cases of overdosage with omeprazole.[1] The major clinical features were drowsiness, headache (possibly due to a metabolite), and tachycardia. Both patients recovered uneventfully without specific treatment.

1. Ferner RE, Allison TR. Omeprazole overdose. *Hum Exp Toxicol* 1993; **12:** 541–2.

Precautions

Before giving omeprazole or other proton pump inhibitors to patients with gastric ulcers the possibility of malignancy should be excluded since these drugs may mask symptoms and delay diagnosis. Omeprazole and other proton pump inhibitors should be used with caution in hepatic impairment and dose adjustment may be required.

Gastric carcinoma. Proton pump inhibitors relieve dyspeptic symptoms associated with gastric carcinoma and can therefore delay its diagnosis. In addition, there is some evidence that they

may also endoscopically 'heal' early gastric carcinoma so that the diagnosis is missed.[1] Consequently, some commentators recommend that proton pump inhibitors should not be prescribed for symptom control before endoscopy in patients at risk for gastric carcinoma.[2]

1. Wayman J, *et al.* The response of early gastric cancer to proton-pump inhibitors. *N Engl J Med* 1998; **338:** 1924–5.
2. Griffin SM, Raimes SA. Proton pump inhibitors may mask early gastric cancer: dyspeptic patients over 45 should undergo endoscopy before these drugs are started. *BMJ* 1998; **317:** 1606–7.

Helicobacter infection. Treatment with proton pump inhibitors may cause false-negative results in the urea breath test for *Helicobacter pylori* infection. In one study in patients with *H. pylori* infection, 4 weeks of treatment with lansoprazole 30 mg daily caused 33% of patients to have negative urea breath tests.[1] The breath test became positive again in all patients within 2 weeks of stopping lansoprazole therapy. In a similar study, 52% of patients had negative urea breath tests for *H. pylori* while receiving omeprazole 20 mg daily, and the breath test became positive again in all patients within 2 to 6 days of stopping treatment.[2] The manufacturers of the urea breath test for *H. pylori* recommend that it should not be performed for at least 2 weeks after stopping treatment with an antisecretory drug.

For a discussion of the link between proton pump inhibitors, *H. pylori*, and gastritis, see under Gastrointestinal Tumours above.

1. Laine L, *et al.* Effect of proton-pump inhibitor therapy on diagnostic testing for Helicobacter pylori. *Ann Intern Med* 1998; **129:** 547–50.
2. Connor SJ, *et al.* The effect of dosing with omeprazole on the accuracy of the C-urea breath test in Helicobacter pylori-infected subjects. *Aliment Pharmacol Ther* 1999; **13:** 1287–93.

Hepatic impairment. In patients with cirrhosis an increase in omeprazole bioavailability, and elimination half-life has been reported.[1] For dosage adjustment in hepatic impairment see Administration in Hepatic Impairment, below.

1. Andersson T, *et al.* Pharmacokinetics of [C]omeprazole in patients with liver cirrhosis. *Clin Pharmacokinet* 1993; **24:** 71–8.

Pregnancy. Proton pump inhibitors are not generally licensed for use during pregnancy (although the UK has licensed omeprazole for such use), but a meta-analysis[1] of 5 studies of exposure to proton pump inhibitors during the first trimester, involving 593 exposed infants, found the relative risk of major abnormalities associated with such exposure to be only 1.18, with a 95% confidence interval ranging from 0.72 to 1.94. Meta-analysis of exposures to omeprazole (from 4 studies only) gave a relative risk of 1.05 (95% confidence interval 0.59 to 1.85). It was concluded that exposure to proton pump inhibitors, and omeprazole in particular, did not pose an important teratogenic risk. A retrospective epidemiological study of data from the Swedish Medical Birth Registry, which identified 955 exposed infants, also found no evidence of significant risk after exposure to omeprazole during pregnancy.[2]

1. Nikfar S, *et al.* Use of proton pump inhibitors during pregnancy and rates of major malformations: a meta-analysis. *Dig Dis Sci* 2002; **47:** 1526–9.
2. Källén BAJ. Use of omeprazole during pregnancy–no hazard demonstrated in 955 infants exposed during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2001; **96:** 63–8.

Interactions

Omeprazole and other proton pump inhibitors are metabolised by the cytochrome P450 system, primarily by isoenzyme CYP2C19, and to a smaller extent by CYP3A4. Inhibitors or inducers of these isoenzymes may affect exposure to omeprazole and other proton pump inhibitors. In turn, proton pump inhibitors may alter the metabolism of some drugs metabolised by these enzymes. Omeprazole may prolong the elimination of diazepam, phenytoin, and warfarin (but see below). Omeprazole and other proton pump inhibitors can reduce the absorption of drugs such as dasatinib, ketoconazole, and itraconazole, whose absorption is dependent on an acid gastric pH. With voriconazole, the plasma concentration of both drugs may be increased (for further information, see below). Other proton pump inhibitors may be similarly affected by voriconazole. Omeprazole and other proton pump inhibitors should not be used with atazanavir, as it substantially reduces exposure to atazanavir.For further information on interactions between proton pump inhibitors and HIV-protease inhibitors, see Table 1, under Antivirals, p.917.

◊ Omeprazole is metabolised primarily by the cytochrome P450 isoenzyme CYP2C19 (see Metabolism, below) and therefore may interact with diazepam (see under Gastrointestinal Drugs, p.991). Some metabolism of phenytoin (see p.500), tolbutamide, and the *R*-enantiomer of warfarin (see p.1430) also takes place by CYP2C19, but the effects seen have been minor.[1] Although some induction of CYP1A2, which metabolises caffeine and theophylline (p.1145), has been reported this does not appear to be clinically significant.[2] While some consider the effect of omeprazole on CYP3A4 activity to be insignificant,[3] others have noted an increasing body of evidence that competitive inhibition of intestinal CYP3A4 by omeprazole may affect the first-pass metabolism of a number of drugs.[4] A review concluded that, while omeprazole and possibly esomeprazole have a considerable potential for drug interactions, lansoprazole, pantoprazole and rabeprazole are associated with a lower incidence of drug interactions.[4]

For a study *in vitro* suggesting that omeprazole affected CYP3A4 metabolism of tacrolimus, see under Interactions of Tacrolimus, p.1845. For more on the effect of proton pump inhibitors on tacrolimus, see Gastrointestinal Drugs, p.1845.

For reference to the possibility of enhanced digoxin absorption with omeprazole, see p.1262. For a study suggesting that omeprazole reduces the absorption of cyanocobalamin and vitamin C, see Malabsorption, above, and for its effect on calcium absorption see p.1714. For reference to possible interactions between methotrexate and omeprazole, see p.748.

1. Andersson T. Pharmacokinetics, metabolism and interactions of acid pump inhibitors: focus on omeprazole, lansoprazole and pantoprazole. *Clin Pharmacokinet* 1996; **31:** 9–28.
2. Rizzo N, *et al.* Omeprazole and lansoprazole are not inducers of cytochrome P4501A2 under conventional therapeutic conditions. *Eur J Clin Pharmacol* 1996; **49:** 491–5.
3. Tateishi T, *et al.* Omeprazole does not affect measured CYP3A4 activity using the erythromycin breath test. *Br J Clin Pharmacol* 1995; **40:** 411–12.
4. Blume H, *et al.* Pharmacokinetic drug interaction profiles of proton pump inhibitors. *Drug Safety* 2006; **29:** 769–84.

Clarithromycin. Studies in healthy subjects have indicated that use of omeprazole with clarithromycin results in an approximate 30% increase in peak plasma concentrations of omeprazole, and an increase in its mean half-life from 1.2 to 1.6 hours.[1] At the same time, plasma concentrations of clarithromycin were also modestly increased, as were local concentrations in gastric tissue and mucus.[1] Clarithromycin inhibits[2] the metabolism of omeprazole mediated by the cytochrome P450 isoenzyme CYP3A4. The interaction may contribute to the benefits of combined therapy for *Helicobacter pylori* infection.

1. Gustavson LE, *et al.* Effect of omeprazole on concentrations of clarithromycin in plasma and gastric tissue at steady state. *Antimicrob Agents Chemother* 1995; **39:** 2078–83.
2. Furuta T, *et al.* Effects of clarithromycin on the metabolism of omeprazole in relation to CYP2C19 genotype status in humans. *Clin Pharmacol Ther* 1999; **66:** 265–74.

Fluvoxamine. Omeprazole and other proton pump inhibitors are metabolised mainly by cytochrome P450 isoenzyme CYP2C19, which shows genetically determined polymorphism, yielding extensive metabolisers and poor metabolisers. Fluvoxamine increased exposure to omeprazole, lansoprazole, and rabeprazole in patients who were extensive metabolisers, but had no effect on pharmacokinetic parameters in poor metabolisers.[1-3] Dose reductions may need to be considered in patients treated with fluvoxamine and proton pump inhibitors.

1. Yasui-Furukori N, *et al.* Different inhibitory effect of fluvoxamine on omeprazole metabolism between CYP2C19 genotypes. *Br J Clin Pharmacol* 2004; **57:** 487–94.
2. Yasui-Furukori N, *et al.* Effects of fluvoxamine on lansoprazole pharmacokinetics in relation to CYP2C19 genotypes. *J Clin Pharmacol* 2004; **44:** 1223–9.
3. Uno T, *et al.* Different effects of fluvoxamine on rabeprazole pharmacokinetics in relation to CYP2C19 genotype status. *Br J Clin Pharmacol* 2006; **61:** 309–14.

Voriconazole. When omeprazole is given with voriconazole, exposure to both drugs is increased. UK licensed product information for omeprazole states that a dose adjustment of omeprazole is not routinely indicated, unless patients have severe hepatic impairment and long-term therapy is indicated. However, UK licensed product information for voriconazole states that, while no dosage adjustment is considered necessary for voriconazole, when patients already receiving omeprazole are started on voriconazole, the dose of omeprazole should be halved. Other proton pump inhibitors may be similarly affected by voriconazole.

Pharmacokinetics

Omeprazole is rapidly but variably absorbed after oral doses. Absorption is not significantly affected by food. Omeprazole is acid-labile and the pharmacokinetics of the various formulations developed to improve oral bioavailability may vary. The absorption of omeprazole also appears to be dose-dependent; increasing the dosage above 40 mg has been reported to increase the plasma concentrations in a non-linear fashion because of saturable first-pass hepatic metabolism. In addition, bioavailability is higher after long-term use.

Bioavailability of omeprazole may be increased in elderly patients, in some ethnic groups such as Chinese, and in patients with hepatic impairment, but is not markedly affected in patients with renal impairment.

On absorption, omeprazole is almost completely metabolised in the liver, primarily by the cytochrome P450 isoenzyme CYP2C19 to form hydroxy-omeprazole, and to a small extent by CYP3A4 to form omeprazole sulfone. The metabolites are inactive, and are excreted mostly in the urine and to a lesser extent in bile. The elimination half-life from plasma is reported to be about 0.5 to 3 hours. Omeprazole is about 95% bound to plasma proteins.

◊ References.

1. Andersson T, *et al.* Pharmacokinetics of various single intravenous and oral doses of omeprazole. *Eur J Clin Pharmacol* 1990; **39:** 195–7.
2. Andersson T, Regårdh C-G. Pharmacokinetics of omeprazole and metabolites following single intravenous and oral doses of 40 and 80 mg. *Drug Invest* 1990; **2:** 255–63.
3. Ching MS, *et al.* Oral bioavailability of omeprazole before and after chronic therapy in patients with duodenal ulcer. *Br J Clin Pharmacol* 1991; **31:** 166–70.
4. Landahl S, *et al.* Pharmacokinetic study of omeprazole in elderly healthy volunteers. *Clin Pharmacokinet* 1992; **23:** 469–76.
5. Andersson T, *et al.* Pharmacokinetics of [C]omeprazole in patients with liver cirrhosis. *Clin Pharmacokinet* 1993; **24:** 71–8.
6. Jacqz-Aigrain E, *et al.* Pharmacokinetics of intravenous omeprazole in children. *Eur J Clin Pharmacol* 1994; **47:** 181–5.
7. Litalien C, *et al.* Pharmacokinetics of proton pump inhibitors in children. *Clin Pharmacokinet* 2005; **44:** 441–66.
8. Fock KM, *et al.* Proton pump inhibitors: do differences in pharmacokinetics translate into differences in clinical outcomes? *Clin Pharmacokinet* 2008; **47:** 1–6.

Metabolism. The major enzyme involved in omeprazole metabolism is cytochrome P450 isoenzyme CYP2C19. This enzyme is polymorphically expressed, and individuals who are deficient in the enzyme are poor metabolisers of omeprazole. This occurs in about 3% of Caucasians and 15% of Chinese, Japanese, and Koreans. These individuals have markedly higher plasma concentrations of omeprazole, and they may require dosage adjustment. Some omeprazole is metabolised by CYP3A4, and some by CYP2D6 to form desmethylomeprazole.

References.

1. Andersson T, *et al.* Identification of human liver cytochrome P450 isoforms mediating omeprazole metabolism. *Br J Clin Pharmacol* 1993; **36:** 521–30.
2. Caraco Y, *et al.* Ethnic and genetic determinants of omeprazole disposition and effect. *Clin Pharmacol Ther* 1996; **60:** 157–67.
3. Karam WG, *et al.* Human CYP2C19 is a major omeprazole 5-hydroxylase, as demonstrated with recombinant cytochrome P450 enzymes. *Drug Metab Dispos* 1996; **24:** 1081–7.

Uses and Administration

Omeprazole is a proton pump inhibitor. It suppresses secretion of gastric acid by inhibiting the enzyme system of hydrogen/potassium adenosine triphosphatase (H^+/K^+ ATPase), the 'proton pump' of the gastric parietal cell. It is used in conditions where inhibition of gastric acid secretion may be beneficial, including aspiration syndromes (p.1693), dyspepsia (below), gastro-oesophageal reflux disease (p.1696), peptic ulcer disease (p.1702), and the Zollinger-Ellison syndrome (p.1704).

Esomeprazole (p.1729), an isomer of omeprazole, is also used.

Omeprazole may be given orally as the base or magnesium salt, or intravenously as the sodium salt. Doses are expressed in terms of the base. Omeprazole magnesium 10.32 mg and omeprazole sodium 10.64 mg are each equivalent to about 10 mg of omeprazole.

For the relief of acid-related **dyspepsia** omeprazole is given in usual doses of 10 or 20 mg daily orally for 2 to 4 weeks.

The usual dose for the treatment of **gastro-oesophageal reflux disease** is 20 mg orally once daily for 4 weeks, followed by a further 4 to 8 weeks if not fully healed. In refractory oesophagitis, a dose of 40 mg daily may be used. Maintenance therapy after healing of oesophagitis is 20 mg once daily, and for acid reflux is 10 mg daily. For dosage in children see below.

In the management of **peptic ulcer disease** a single daily dose of 20 mg orally, or 40 mg in severe cases, is given. Treatment is continued for 4 weeks for duodenal ulcer and 8 weeks for gastric ulcer. Where appropriate, a dose of 10 to 20 mg once daily may be given for maintenance.

For the eradication of *Helicobacter pylori* in peptic ulceration omeprazole may be combined with antibacterials in dual or triple therapy. Effective **triple therapy** regimens include omeprazole 20 mg twice daily or 40 mg once daily combined with: amoxicillin 500 mg and metronidazole 400 mg, both three times daily; clarithromycin 250 mg and metronidazole 400 mg (or tinidazole 500 mg) both twice daily; or with amoxicil-

lin 1 g and clarithromycin 500 mg, both twice daily. These regimens are given for 1 week. **Dual therapy** regimens such as omeprazole 20 mg twice daily or 40 mg daily with either amoxicillin 750 mg to 1 g twice daily or clarithromycin 500 mg three times daily, are less effective and must be given for 2 weeks. Omeprazole alone may be continued for a further 4 to 8 weeks.

Doses of 20 mg daily orally are used in the treatment of **NSAID-associated ulceration**; a dose of 20 mg daily may also be used for prophylaxis in patients with a history of gastroduodenal lesions who require continued NSAID treatment.

The initial recommended dosage for patients with the **Zollinger-Ellison syndrome** is 60 mg orally once daily, adjusted as required. The majority of patients are effectively controlled by doses in the range 20 to 120 mg daily, but doses up to 120 mg three times daily have been used. Daily doses above 80 mg should be given as divided doses (usually 2).

Omeprazole is also used for the prophylaxis of **acid aspiration** during general anaesthesia, in a dose of 40 mg the evening before surgery and a further 40 mg two to six hours before the procedure.

The dose of omeprazole may need to be reduced in patients with hepatic impairment (see below).

PARENTERAL DOSAGE.

In patients who are unsuited to receive oral therapy omeprazole sodium may be given on a short-term basis by intravenous infusion, in a usual dose equivalent to 40 mg of the base over a period of 20 to 30 minutes in 100 mL of sodium chloride 0.9% or glucose 5%. It may also be given by slow intravenous injection. Higher intravenous doses have been given to patients with Zollinger-Ellison syndrome.

◊ General reviews.

1. Richardson P, *et al.* Proton pump inhibitors: pharmacology and rationale for use in gastrointestinal disorders. *Drugs* 1998; **56:** 307–35.
2. Langtry HD, Wilde MI. Omeprazole: a review of its use in Helicobacter pylori infection, gastro-oesophageal reflux disease and peptic ulcers induced by nonsteroidal anti-inflammatory drugs. *Drugs* 1998; **56:** 447–86.
3. Berardi RR, Welage LS. Proton-pump inhibitors in acid-related diseases. *Am J Health-Syst Pharm* 1998; **55:** 2289–98.
4. Brown GJE, Yeomans ND. Prevention of the gastrointestinal adverse effects of nonsteroidal anti-inflammatory drugs: the role of proton pump inhibitors. *Drug Safety* 1999; **21:** 503–12.
5. Erstad BL. Proton-pump inhibitors for acute peptic ulcer bleeding. *Ann Pharmacother* 2001; **35:** 730–40.
6. Robinson M, Horn J. Clinical pharmacology of proton pump inhibitors: what the practising physician needs to know. *Drugs* 2003; **63:** 2739–54.
7. Dekel R, *et al.* The role of proton pump inhibitors in gastro-oesophageal reflux disease. *Drugs* 2004; **64:** 277–95.
8. Anonymous. Proton pump inhibitors for GERD in children. *Med Lett Drugs Ther* 2007; **49:** 17–18.

Administration. Omeprazole is given orally as tablets or capsules containing enteric-coated pellets or granules, which should be swallowed whole and not crushed or chewed. In children or patients with swallowing difficulties, UK licensed product information (*Losec; AstraZeneca*) states that the tablet be dispersed in water and then mixed with fruit juice (with a pH less than 5) or yogurt before swallowing without chewing. Similarly the contents of the capsules can be mixed with water, fruit juice (with a pH less than 5) or yogurt and swallowed without chewing. A mixture of omeprazole and sodium bicarbonate as a powder for oral suspension is available in some countries.

Administration in children. Licensed UK *oral* doses of omeprazole for the treatment of gastro-oesophageal reflux disease in children 1 year of age and over are determined by body-weight as follows:

- 10 to 20 kg: 10 mg once daily
- over 20 kg: 20 mg once daily

These doses may be doubled if necessary. Treatment may be given for 4 to 12 weeks.

For gastro-oesophageal reflux disease, acid-related dyspepsia, treatment of duodenal and benign gastric ulcers including NSAID-associated ulceration, prophylaxis of acid aspiration, and Zollinger-Ellison syndrome, the *BNFC* recommends an oral dose of 700 micrograms/kg once daily in neonates and children 1 month to 2 years of age. If needed, doses may be increased in neonates after 7 to 14 days, to 1.4 mg/kg once daily; some neonates may require up to 2.8 mg/kg once daily. Children's doses may be increased up to 3 mg/kg (to a maximum of 20 mg) once daily.

For *parenteral* dosage in children the *BNFC* recommends an intravenous dose of 500 micrograms/kg (to a maximum of 20 mg) once daily in children aged 1 month to 12 years; this may be increased to 2 mg/kg (to a maximum of 40 mg) once daily if needed.

For the eradication of *Helicobacter pylori* in children, the *BNFC* recommends an oral dose of omeprazole 1 to 2 mg/kg (to a maximum dose of 40 mg) once daily. This is given with antibacterial therapy under specialist supervision.

For administration of the tablets or capsules to children, see Administration, above.

Administration in hepatic impairment. Bioavailability and half-life of omeprazole can increase in patients with hepatic impairment. UK licensed product information recommends that a maximum daily oral dose of 20 mg be used in these patients; a daily intravenous dose of 10 to 20 mg is considered sufficient.

Asthma. Gastro-oesophageal reflux has been suggested as a potential exacerbating factor for asthma (p.1108), and acid suppressive therapy with omeprazole has been reported to reduce asthma symptoms in some[1] but not other[2] studies. A meta-analysis of acid suppressive therapy concluded it was not effective in improving asthma symptoms in most patients with gastro-oesophageal reflux,[3] and the link between reflux and asthma symptoms has been disputed.[4]

1. Harding SM, *et al.* Asthma and gastroesophageal reflux: acid suppressive therapy improves asthma outcome. *Am J Med* 1996; **100:** 395–405.
2. Ford GA, *et al.* Omeprazole in the treatment of asthmatics with nocturnal symptoms and gastro-oesophageal reflux: a placebo-controlled cross-over study. *Postgrad Med J* 1994; **70:** 350–4.
3. Gibson PG, *et al.* Gastro-oesophageal reflux treatment for asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 11/12/07).
4. Field SK. A critical review of the studies of the effects of simulated or real gastroesophageal reflux on pulmonary function in asthmatic adults. *Chest* 1999; **115:** 848–56.

Dyspepsia. Although earlier UK guidelines on the use of proton pump inhibitors in dyspepsia (p.1695) suggested that they should not be used routinely in non-ulcer dyspepsia,[1] subsequent guidelines on its general management in both the UK[2] and the US[3] consider that a 1-month empirical trial in patients aged under 55 without symptoms suggestive of more serious disease is a valid first-line treatment.

1. NICE. Guidance on the use of proton pump inhibitors in the treatment of dyspepsia (issued July 2000). Available at: http://www.nice.org.uk/nicemedia/pdf/proton.pdf (accessed 11/02/08)
2. NICE. Dyspepsia: management of dyspepsia in adults in primary care (Clinical Guideline 17: issued August 2004, updated June 2005). Available at: http://www.nice.org.uk/nicemedia/pdf/CG017NICEguideline.pdf (accessed 11/02/08)
3. American Gastroenterological Association. American Gastroenterological Association medical position statement: evaluation of dyspepsia. *Gastroenterology* 2005; **129:** 1753–5. Also available at: http://download.journals.elsevierhealth.com/pdfs/journals/0016-5085/PIIS0016508505018172.pdf (accessed 11/02/08)

Inflammatory bowel disease. There are a few reports[1-3] of responses to omeprazole in patients with inflammatory bowel disease (p.1697). Combination of omeprazole with mesalazine has also been tried.[2]

1. Heinzow U, Schlegelberger T. Omeprazole in ulcerative colitis. *Lancet* 1994; **343:** 477.
2. Dickinson JB. Is omeprazole helpful in inflammatory bowel disease? *J Clin Gastroenterol* 1994; **18:** 317–19.
3. Guslandi M, Tittobello A. Symptomatic response to omeprazole in inflammatory bowel disease. *J Clin Gastroenterol* 1996; **22:** 159–60.

Scleroderma. Gastro-oesophageal reflux is one of the gastrointestinal manifestations of systemic sclerosis, and proton pump inhibitors such as omeprazole play a major role in the management of such gastrointestinal disease.[1] For a discussion of the broader management of the condition see p.1817.

1. Williamson DJ. Update on scleroderma. *Med J Aust* 1995; **162:** 599–601.

Preparations

BP 2008: Gastro-resistant Omeprazole Capsules; Gastro-resistant Omeprazole Tablets;
USP 31: Omeprazole Delayed-Release Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Acimed; Aziatop; Brux; Danlox; Fabrazol; Fendiprazol; Gastec; Gastroprazol; Gastrotem; Klomeprax; Losec; Mucoxol; Omeprasec; Pepticus†; Pravil; Procelac; Prysma; Regulacid; Timezol; Ulcozol; Zoltenk; ***Austral.:*** Acimax; Losec; Maxor†; Meprazol; Omepral; Probitor; ***Austria:*** Helicostad; Losec; Lostad; Medoprazol; Omec; Omegastron; Omepralan; Probitor†; Semiglen†; ***Belg.:*** Docomepra; Logastric; Losec; Omepratop; Sedacid; ***Braz.:*** Belprazol†; Bioprazol†; Elprazol†; Estomepe; Eupept; Fegran†; Gasec; Gaspiren; Gastrib†; Gastrium; Gastrozol; Klispel; Lomepral†; Loprazol; Losaprol†; Losar†; Losec; Lozap†; Lozeprel; Lozix†; Meprazan; Mesopran†; Neoprazol; Novoprazol†; Omegastrol; Omenax; Omep†; Omepramed; Omeprazin; Omeprotec†; Oprazon; Peprazol; Pepsicaps; Prazolex; Prazonil; Prazotom†; Ulcecaps†; Ulcefor; Ulcozol†; Uniprazol; Victrix; Zolpramex†; ***Canad.:*** Losec; ***Chile:*** Lomex; Losec; Micromex; Omeprax; Pepticum†; Prazolo†; Ulc-Out; Ulcelac; Ulcrux†; Zatrol; Zomepral; ***Cz.:*** Apo-Ome; Gasec; Helicid; Lomac; Losec; Loseprazol; Omepirex; Omeprol; Omolin; Onprelen; Oprazole†; Ortanol; Pepticum†; Problok†; Tulzol; Ultop; ***Denm.:*** Losec; ***Fin.:*** Losec; ***Fr.:*** Mopral; Zoltum; ***Ger.:*** Antra; Gastracid; Ome TAD; Ome-nerton; Ome-Puren; Ome-Q; Omebeta; Omedoc; Omegamma; OmeLich; Omelind; Omep; ***Gr.:*** Assoprol; Belifax; Elibactin; Elkostop; Elkotheran; Eselan; Esopraz; Ezipol; Gertalgin; Glaveral; Inhiplex; Kerlofin; Lanex; Lenar; Lomezec; Loproc; Lordin; Losec; Lozaprin; Malortil; Meprolen; Novek; Odamesol; Odasol; Ofnimarex; Omeprol; Penrazol; Pipacid; Prazolin; Probitor; Rythmogastryl; Sedacid; Sieral; Silato; Ufonitren; Veralox; Zolldenol; ***Hong Kong:*** Losec; ***Hung.:*** Losec; Omegen; Omep; Omeprawin; Ulzol; ***India:*** Biocid; Lomac; Nogacid; Ocid; Olit; Omezol; Promisec; Ulzol†; ***Indon.:*** Contral; Dudencer; Loklor; Losec; Meisec; Norsec; Omevell; OMZ; Onic; Opm; Oprezol; Ozid; Prohibit; Promezol; Protop; Pumpitor; Redusec; Regasec; Rocer; Socid; Stomacer; Ulzol; Zepral; Zollocid; ***Irl.:*** BySec; Lopraz; Losamel; Losec; Losepine; Ulcid; ***Israel:*** Losec; Omepradex; ***Ital.:*** Antra; Losec; Mepral; Omeprazen; ***Jpn:*** Omepral; ***Malaysia:*** Gasec; Losec; Medoprazole; Omelon; Omesec; Omez; Omezole; Probitor†; Romesec; Zenpro†; Zimor; ***Mex.:*** Alboz; Aleprozil; Apopraza; Argaryn†; Azoran; Danovag; Domer; Gerdex; Grizol; Hopram†; Ibax; Inhibitron; Logazil; Lopram; Losec; Medral; Mopral; Mornin; Olexin; Omecaps; Ometec; Opramid; Osiren; Ozoken; Panzer; Pastrizol; Pentren; Prazidec; Prazolit; Sarox; Solcer; Suifac; Tarzol; Ucetal; Ulsen; Ultizol; Ultromep; Usaltron; Vulcasid; Zoral; Zulmedx; ***Neth.:*** Losec; Omeprazostad†; Omepstad†; Omezol†; Omolin; Romisan; ***Norw.:*** Losec; ***NZ:*** Losec; Omezol; ***Philipp.:*** Gastriloc; Hovizol; Losec; Mepracid; Omenole; Omepron; Omizac; OMZ; Opehex; Peptisolv; Premio; Promesec; Puroxel; Risek; Tansinel; Ulsek; Zyom; ***Pol.:*** Bioprazol; Gasec; Helicid; Losec; Notis; Omar; Ortanol; Polprazol; Prazol; Ulzol; ***Port.:*** Belmazol; Bloprazol; Eugastrim; Gasec; Losec; Mepraz; Novek; Nuclosina†; Omepra; Omeratio; Omerol†; Ometon; Omezolan; Prazentol; Prazex; Prazolene; Proclor; Proton; ***Rus.:*** Gastrozol (Гастрозол); Helicid (Хеликид); Helol (Хелол); Losec (Лосек); Ocid (Оцид); Omez (Омез); Omipix (Омипикс); Omitox (Омитокс); Omizac (Омизак); Romesec (Ромесек); Sopral (Сопрал)†; Ultop (Ультоп); Ulzol (Улзол); Zerocid (Зероцид); ***S.Afr.:*** Altosec; Losec; Omez; Omiloc; Ulzec; ***Singapore:*** Losec; Ocid; Olit; Omesec; Omezole; Penrazole; Proceptin; Romesec; Zenpro; Zimor; ***Spain:*** Audazol; Aulcer; Belmazol; Ceprandal; Dolintol; Elgam; Emeproton; Gastrimut; Indurgan; Ipirasa; Losec; Miol; Mopral†; Norpramin; Novek; Nuclosina; Omapren; Ompranyt; Parizac; Pepticum; Prysma; Sanamidol; Ulceral; Ulcesep; Ulcometion; Zimor; ***Swed.:*** Losec; ***Switz.:*** Amanol; Antra; Antramups; Gastroprazol; Omed; omepra-basan†; Omezol; Oprazol; ***Thai.:*** Airomet; Desec; Dosate; Duogas; Eselan; Eucid; Gaster; Gomec; Lomac; Losec; Madiprazole; Meiceral; Metsec; Miracid; Nocid; O-Sid; Olit; Omez; Omicap; Oprazole; Probitor; Severon†; Stomec; Ulprazole; Zefxon; Zimor†; ***Turk.:*** Demeprazol; Erbolin; Losec; Omegast; Omeprazid; Omeprol; Prosek; ***UAE:*** Risek; ***UK:*** Heartburn Relief; Losec; Zanprol; ***USA:*** Prilosec; ***Venez.:*** Fordex; Gastronol; Losec; Meprox†; Omebloc; Omevax; Omez†; Omezul; Parsolen; Prazol†; Probitor; Promezol; Tecol†.

Multi-ingredient: ***Austral.:*** Klacid HP 7; Losec Hp 7; ***Braz.:*** Erradic; Helicocid Triplice†; Omepramix; ***Canad.:*** Losec 1-2-3 A; Losec 1-2-3 M; ***Fin.:*** Losec Helira†; ***India:*** Helipac; Nogacid D; Okacid D; OTC HP Kit; ***Malaysia:*** Pylobact Combi; ***NZ:*** Klacid HP 7†; Losec Hp 7; ***Philipp.:*** OAC Hp7; ***Rus.:*** Pylobact (Пилобакт); ***S.Afr.:*** Losec 20 Triple†; ***USA:*** Zegerid.

Ondansetron *(BAN, rINN)*

GR-38032; Ondansétron; Ondansetrón; Ondansetroni; Ondansetronum. (±)-1,2,3,9-Tetrahydro-9-methyl-3-(2-methylimidazol-1-ylmethyl)-carbazol-4(9*H*)-one.

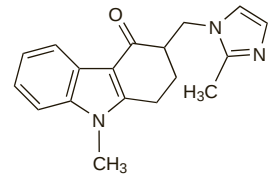
Ондансетрон

$C_{18}H_{19}N_3O$ = 293.4.

CAS — 99614-02-5; 116002-70-1.

ATC — A04AA01.

ATC Vet — QA04AA01.



Pharmacopoeias. In *US*.

USP 31 (Ondansetron). A white to off-white powder. Sparingly soluble in water; very soluble in acid solutions. Store in airtight containers. Protect from light.

Ondansetron Hydrochloride *(BANM, USAN, rINNM)*

GR-38032F; Hidrocloruro de ondansetrón; Ondansétron, chlorhydrate d'; Ondansetron hydrochlorid; Ondansetronhydroklorid; Ondansetroni hydrochloridum; Ondansetronihydrokloridi; Ondansetrono hidrochloridas; Ondanstroni Hydrochloridum; Ondánszetronhidroklorid; SN-307.

Ондансетрона Гидрохлорид

$C_{18}H_{19}N_3O,HCl,2H_2O$ = 365.9.

CAS — 99614-01-4; 103639-04-9.

ATC — A04AA01.

ATC Vet — QA04AA01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US*.

Ph. Eur. 6.2 (Ondansetron Hydrochloride Dihydrate). A white or almost white powder. Sparingly soluble in water and in alcohol; slightly soluble in dichloromethane; soluble in methyl alcohol. Protect from light.

USP 31 (Ondansetron Hydrochloride). A white to off-white powder. Sparingly soluble in water and in alcohol; very slightly soluble in acetone, in chloroform, and in ethyl acetate; slightly soluble in dichloromethane and in isopropyl alcohol; soluble in methyl alcohol. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. Ondansetron hydrochloride and dexamethasone sodium phosphate were not compatible when high concentrations were combined in polypropylene syringes.[1] Lower concentrations (up to 640 micrograms/mL of ondansetron and 400 micrograms/mL of dexamethasone phosphate) were stable