er conditions where inhibition of gastric acid secretion may be beneficial.

Lansoprazole is usually given orally as capsules, dispersible tablets, or suspension containing enteric-coated granules. Once daily regimens are taken before food in the morning. An intravenous formulation is also available.

For the relief of acid-related **dyspepsia** (p.1695) intermittent courses of lansoprazole may be given in doses of 15 or 30 mg once daily, for 2 to 4 weeks.

In the treatment of **gastro-oesophageal reflux disease** (p.1696) the dose is 15 to 30 mg once daily for 4 to 8 weeks; thereafter maintenance therapy can be continued with 15 or 30 mg once daily according to response. In patients unable to take oral therapy, lansoprazole may be given by intravenous infusion for the treatment of erosive oesophagitis for up to 7 days; a dose of 30 mg over 30 minutes daily is recommended.

Lansoprazole is given for the treatment of **peptic ulcer disease** (p.1702) in the UK in doses of 30 mg once daily. Treatment is continued for 2 to 4 weeks for duodenal and 4 to 8 weeks for gastric ulcer. In the USA, a dose of 15 mg daily for 4 weeks is recommended for duodenal ulcer, and 30 mg once daily is given for up to 8 weeks for gastric ulceration. When appropriate, 15 mg daily may be used as maintenance therapy for the prevention of relapse of duodenal ulcer. Lansoprazole may be combined with antibacterials in one-week **triple therapy** regimens for the eradication of *Helicobacter pylori*. Effective regimens include lansoprazole 30 mg twice daily combined with clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily, or combined with clarithromycin 250 mg twice daily and metronidazole 400 mg twice daily; lansoprazole with amoxicillin and metronidazole has also been used. In patients with **NSAID-associated ulceration** a dose of 30 mg daily for 4 to 8 weeks is recommended; 15 to 30 mg daily may be used as prophylaxis for patients who require continued NSAID treatment.

In the treatment of pathological hypersecretory states such as the **Zollinger-Ellison syndrome** (p.1704) the initial dose is 60 mg once daily, adjusted as required. Doses of up to 90 mg twice daily have been used. Daily doses greater than 120 mg should be given in divided doses.

In the USA, **children** aged from 1 to 11 years may be given lansoprazole for the short-term treatment of erosive oesophagitis and symptomatic gastro-oesophageal reflux disease. Children weighing 30 kg or less should be given 15 mg once daily, and those weighing more than 30 kg are given 30 mg once daily, for up to 12 weeks. Doses of up to 30 mg twice daily have been used. In children aged from 12 to 17 years, lansoprazole 30 mg once daily for up to 8 weeks may be used for erosive oesophagitis, and 15 mg once daily for up to 8 weeks may be used for symptomatic gastro-oesophageal reflux disease. Although not licensed for children in the UK, the *BNFC* recommends comparable oral daily doses of 0.5 to 1 mg/kg in children up to 30 kg in weight, and 15 or 30 mg once daily in those over 30 kg.

Doses of lansoprazole may need to be reduced in patients with hepatic impairment (see below).

◊ General references. For general reviews of proton pump inhibitors, see Omeprazole, p.1756.

1. Langtry HD, Wilde MI. Lansoprazole: an update of its pharmacological properties and clinical efficacy in the management of acid-related disorders. *Drugs* 1997; **54:** 473–500.
2. Matheson AJ, Jarvis B. Lansoprazole: an update of its place in the management of acid-related disorders. *Drugs* 2001; **61:** 1801–33.
3. Freston JW, *et al.* Lansoprazole for maintenance of remission of erosive oesophagitis. *Drugs* 2002; **62:** 1173–84.
4. Dando TM, Plosker GL. Intravenous lansoprazole: in erosive oesophagitis. *Drugs* 2004; **64:** 2085–9.
5. Croom KF, Scott LJ. Lansoprazole: in the treatment of gastro-oesophageal reflux disease in children and adolescents. *Drugs* 2005; **65:** 2129–35.

Administration. Lansoprazole *capsules* should be swallowed whole and not crushed or chewed. Lansoprazole *dispersible tablets* should be placed on the tongue and allowed to disintegrate and the resultant granules swallowed; alternatively, the tablets may be swallowed whole with a glass of water. The tablets should not be crushed or chewed. The tablets may also be dispersed in a small amount of water and given via an oral syringe, or via a nasogastric tube. Lansoprazole *granules for oral suspension* should be reconstituted in a little water and swallowed immediately. Where the suspension formulation is not available, the contents of the capsules (enteric-coated granules) can be sprinkled on a small amount of soft food (such as yogurt or apple sauce) or mixed with a little fruit juice and swallowed. For administration via a nasogastric tube, the contents of a capsule may be mixed with 40 mL of apple juice; additional apple juice may be used to flush the tube.

Administration in hepatic impairment. Exposure to lansoprazole is increased in patients with hepatic impairment. Licensed product information recommends that patients with moderate to severe liver disease should be kept under supervision, and that the daily dose should be reduced by 50%.

Preparations

USP 31: Lansoprazole Delayed-Release Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Ilsatec†; Lanzopral; Mesactol; Ogasto†; ***Austral.:*** Zoton; ***Austria:*** Agopton; Lansobene; ***Belg.:*** Dakar; ***Braz.:*** Anzoprol†; Lanogastro; Lanz; Lanzol; Lanzopept; Neozol; Ogastro; Prazol; ***Canad.:*** Prevacid; ***Chile:*** Fudermex; Gastride; Lanzopral; Ogasto†; Unival; ***Cz.:*** Lansone†; Lansoprol; Lanzul; ***Denm.:*** Lanzo; ***Fin.:*** Lanzo; Zolt; ***Fr.:*** Lanzor; Ogast; Ogastoro; ***Ger.:*** Agopton; Lanzor; ***Gr.:*** Elcodil; Lanciprol; Lanso; Laprazol; ***Hong Kong:*** Takepron; ***Hung.:*** Lansacid; Lansogen; Lansone; Lansoptol; Levant; Protonexa; Refluxon; ***India:*** Chexid; Lancus; Lanzol; ***Indon.:*** Compraz; Digest; Gastrolan; Inhipraz; Lancid; Lapraz; Laproton; Lasgan; Laz; Loprezol; Nufaprazol; Prazotec; Prolanz; Prosogan; Protica; Pysolan; Solans; Sopralan; Ulceran; ***Irl.:*** Lanziop; Lanzol; Razolager; Zomel; Zoton; Zotrole; ***Israel:*** Lanton; Zoton; ***Ital.:*** Lansox; Limpidex; Zoton; ***Jpn:*** Prevacid; Takepron; ***Malaysia:*** Prevacid; ***Mex.:*** Bonzol; Ilsatec; Imidex; Keval; Lafin; Lanodizol; Mavilan; Mediprim; Ogastro; Olan; Palatrin; Pranix; Safemar; Uldapril; Ulpax; ***Neth.:*** Prezal; ***Norw.:*** Lanzo; ***NZ:*** Solox; Zoton†; ***Philipp.:*** Lanzohex; Prevacid; Pylison; ***Pol.:*** LansoLek; Lanzostad; Lanzul; ***Port.:*** Alexin; Dispepci; Gastrex; Gastrolanzo; Gastroliber; Lansox; Lanzogastro; Lapol; Lizul†; Monolitum†; Ogasto; Pampe; Pepzol†; Ulcertec; ***Rus.:*** Acrilans (Акриланз); Epicur (Эпикур); Helicol (Геликол); Lanzap (Ланзап); ***S.Afr.:*** Adco-Roznal; Lancap; Lansoloc; Lanzor; ***Singapore:*** Prevacid; ***Spain:*** Bamalite; Estomil; Eudiges; Lanzol; Monolitum; Opiren; Pro Ulco; Protoner; ***Swed.:*** Lanzo; ***Switz.:*** Agopton; ***Thai.:*** Prevacid; ***Turk.:*** Aprazol; Degastrol; Helicol; Lansazol; Lansoprol; Lansor; Lanzedin; Ogastro; Opagis; Vogast; Zoprol; ***UAE:*** Lanfast; ***UK:*** Zoton; ***USA:*** Prevacid; ***Venez.:*** Biolanz; Gastrazol; Ilsatec†; Lansovax; Lanzap†; Lanzol; Lanzopral; Ogastro.

Multi-ingredient: ***Arg.:*** Heliklar†; ***Braz.:*** Anzopac†; H-Bacter; Helicopac; Heliklar; Lansodom; Lansoprid; Pylorikit; Pyloripac; Pyloritrat; ***Canad.:*** Hp-Pac; ***Fin.:*** Helipak A; Helipak K; Helipak T; ***India:*** Okalan D; Pylokit; ***Mex.:*** Pylopac; ***Turk.:*** Helipak; ***UK:*** Helicleat†; HeliMet†; ***USA:*** Prevpac.

Used as an adjunct in: ***USA:*** Prevacid NapraPAC.

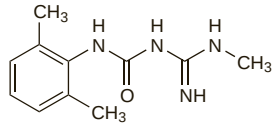
Lidamidine Hydrochloride *(USAN, rINNM)*

Hidrocloruro de lidamidina; Lidamidine, Chlorhydrate de; Lidamidini Hydrochloridum; WHR-1142A. *N*-(2,6-Dimethylphenyl)-*N'*-[imino(methylamino)methyl]urea hydrochloride.

Лидамидина Гидрохлорид

$C_{11}H_{16}N_4O,HCl$ = 256.7.

CAS — 66871-56-5 (lidamidine); 65009-35-0 (lidamidine hydrochloride).



(lidamidine)

Profile
Lidamidine is an alpha$_2$-adrenergic receptor stimulant used as the hydrochloride for the management of diarrhoea and other gastrointestinal disorders.

Preparations
Proprietary Preparations (details are given in Part 3)
Mex.: Idealid†; Supra.

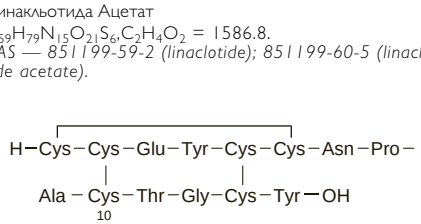
Linaclotide Acetate *(USAN, rINNM)*

Acetato de linaclotida; Linaclotide, Acétate de; Linaclotidi Acetas; MD-1100; MM-416775. [9-L-Tyrosine]heat-stable enterotoxin (Escherichia coli)-(6-19)-peptide monoacetate salt.

Линакльотида Ацетат

$C_{59}H_{79}N_{15}O_{21}S_6,C_2H_4O_2$ = 1586.8.

CAS — 851199-59-2 (linaclotide); 851199-60-5 (linaclotide acetate).



Profile
Linaclotide is a guanylate cyclase-C agonist being studied in the treatment of constipation-predominant irritable bowel syndrome and chronic constipation.

◊ References.

1. Harris LA, Crowell MD. Linaclotide, a new direction in the treatment of irritable bowel syndrome and chronic constipation. *Curr Opin Mol Ther* 2007; **9:** 403–10.
2. Andresen V, *et al.* Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome. *Gastroenterology* 2007; **133:** 761–8.

Liquorice

Alcaçuz; Édesgyökér; Gancao; Glycyrrhiza; Korzeń lukrecji; Lakritsijuuri; Lakritsrot; Lékořicový kořen; Licorice; Liquiritiae radix; Liquorice Root; Orozuz; Raiz de Regaliz; Regaliz; Réglisse, racine de; Saldymedžių šaknys; Süssholzwurzel.

Лакрица

Description. Liquorice is the dried rhizome and roots of *Glycyrrhiza glabra*. Those of *G. glabra* var. *typica* are known in commerce as Spanish Liquorice, those of *G. glabra* var. *glandulifera* as Russian Liquorice, and those of *G. glabra* var. *β-violacea* as Persian Liquorice.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*. *Eur.* (see p.vii) also includes Liquorice Dry Extract for Flavouring Purposes. *US* also includes Powdered Liquorice and Powdered Licorice Extract. *Br.* also includes Liquorice Root for use in Traditional Herbal Medicine and Processed Liquorice Root for use in Traditional Herbal Medicinal Product.

Ph. Eur. 6.2 (Liquorice Root; Liquorice BP 2008). The dried unpeeled or peeled, whole or cut root and stolons of *Glycyrrhiza glabra* and/or *G. inflata* and/or *G. uralensis*. It contains not less than 4% of glycyrrhizic acid. Protect from light.

USP 31 (Licorice). The roots, rhizomes, and stolons of *Glycyrrhiza glabra* or *G. uralensis*. It contains not less than 2.5% of glycyrrhizic acid, calculated on the dried basis. Store in a cool, dry place.

BP 2008 (Liquorice Root for use in THM). It is the dried unpeeled root and rhizome of *Glycyrrhiza uralensis*, *G. inflata*, or *G. glabra*. For use in traditional Chinese medicines. It contains not less than 2.0% of glycyrrhizic acid calculated with reference to the dried material. Protect from moisture.

BP 2008 (Processed Liquorice Root for use in THMP). Liquorice Root for use in THM which has been cleaned, softened, sliced transversely or longitudinally to form uniform pieces, and dried. It contains not less than 2.0% of glycyrrhizic acid calculated with reference to the dried material. Protect from moisture.

Adverse Effects and Precautions
Liquorice has mineralocorticoid-like actions manifesting as sodium and water retention and hypokalaemia (see below).

Deglycyrrhizinised liquorice is not usually associated with such adverse effects.

Mineralocorticoid effects. Mineralocorticoid effects have been reported after excessive or prolonged ingestion of liquorice. The liquorice may be ingested in confectionery (including liquorice-flavoured chewing gum), tea, soft drinks, herbal medicines, cough mixtures, or by chewing tobacco. The enzyme 11-β-hydroxysteroid dehydrogenase (cortisol oxidase) converts cortisol to cortisone, preventing cortisol gaining access to non-specific mineralocorticoid receptors. This enzyme is inhibited by glycyrrhetinic acid (produced by the hydrolysis of glycyrrhizic acid, a natural constituent of liquorice), resulting in increased concentrations of cortisol in the body, enhancing its physiological effects.[1-3]

Clinical manifestations include consequences of sodium retention such as hypertension,[4-10] and hypokalaemia, which can result in neuromuscular disturbances ranging from muscle weakness,[11] myoclonus,[12] and myopathy[10] to paralysis[13-15] and rhabdomyolysis.[15-17] Arrhythmias[16,18] and fatal cardiac arrest[19] have also been reported.

Increased amounts of cortisol in vascular smooth muscle may cause vasoconstriction. Vasospasm of vessels supplying the optic nerve may have caused transient visual disturbances reported after liquorice ingestion.[2]

Other reported effects of liquorice include growth retardation in a boy with Addison's disease;[20] liquorice was thought to have potentiated the effect of hydrocortisone.

Endocrine effects of liquorice have been reviewed.[21] Conflicting effects on testosterone and prolactin have been reported. Components of liquorice root (which has been tried for menopausal symptoms) have both oestrogenic and anti-oestrogenic activity, and it has reportedly caused gynaecomastia.

Individuals vary markedly in their susceptibility to liquorice-induced adverse effects.[1] Those consuming 400 mg glycyrrhetinic acid daily generally experience adverse effects, but a regular daily intake of no more than 100 mg of glycyrrhetinic acid (about 50 g of liquorice sweets) has produced adverse effects in some who appear more sensitive to its effects. Some consider a daily intake of 10 mg glycyrrhetinic acid to be a safe daily dose for adults; the amount of salt consumed needs to be considered as

even a low dose of liquorice may induce sodium overload in those consuming high amounts of sodium chloride.[3]

1. Walker BR, Edwards CR. Licorice-induced hypertension and syndromes of apparent mineralocorticoid excess. *Endocrinol Metab Clin North Am* 1994; **23:** 359–77.
2. Dobbins KRB, Saul RF. Transient visual loss after licorice ingestion. *J Neuroophthalmol* 2000; **20:** 38–41.
3. Frey FJ, Ferrari P. Pastis and hypertension—what is the molecular basis? *Nephrol Dial Transplant* 2000; **15:** 1512–14.
4. van Uum SH. Liquorice and hypertension. *Neth J Med* 2005; **63:** 119–20.
5. Dellow EL, *et al.* Pontefract cakes can be bad for you: refractory hypertension and liquorice excess. *Nephrol Dial Transplant* 1999; **14:** 218–20.
6. Woywodt A, *et al.* Turkish pepper (extra hot). *Postgrad Med J* 2000; **76:** 426–8.
7. Janse A, *et al.* The old lady who liked liquorice: hypertension due to chronic intoxication in a memory-impaired patient. *Neth J Med* 2005; **63:** 149–50.
8. Russo S, *et al.* Low doses of liquorice can induce hypertension encephalopathy. *Am J Nephrol* 2000; **20:** 145–8.
9. Hall RC, Clemett RS. Central retinal vein occlusion associated with liquorice ingestion. *Clin Experiment Ophthalmol* 2004; **32:** 341.
10. Hussain RM. The sweet cake that reaches parts other cakes can't! *Postgrad Med J* 2003; **79:** 115–16.
11. Yoshida S, Takayama Y. Licorice-induced hypokalemia as a treatable cause of dropped head syndrome. *Clin Neurol Neurosurg* 2003; **105:** 286–7.
12. Ishiguchi T, *et al.* Myoclonus and metabolic alkalosis from licorice in antacid. *Intern Med* 2004; **43:** 59–62.
13. Elinav E, Chajek-Shaul T. Licorice consumption causing severe hypokalemic paralysis. *Mayo Clin Proc* 2003; **78:** 767–8.
14. Lin S-H, *et al.* An unusual cause of hypokalemic paralysis: chronic licorice ingestion. *Am J Med Sci* 2003; **325:** 153–6.
15. van den Bosch AE, *et al.* Severe hypokalaemic paralysis and rhabdomyolysis due to ingestion of liquorice. *Neth J Med* 2005; **63:** 146–8.
16. Bauchart J-J, *et al.* Alcohol-free pastis and hypokalaemia. *Lancet* 1995; **346:** 1701.
17. Firenzuoli F, Gori L. Rabdomiolisi da liquirizia. *Recenti Prog Med* 2002; **93:** 482–3.
18. Eriksson JW, *et al.* Life-threatening ventricular tachycardia due to liquorice-induced hypokalaemia. *J Intern Med* 1999; **245:** 307–10.
19. Haberer JP, *et al.* Severe hypokalaemia secondary to overindulgence in alcohol-free "pastis". *Lancet* 1984; **i:** 575–6.
20. Doeker BM, Andler W. Liquorice, growth retardation and Addison's disease. *Horm Res* 1999; **52:** 253–5.
21. Armanini D, *et al.* History of the endocrine effects of licorice. *Exp Clin Endocrinol Diabetes* 2002; **110:** 257–61.

Pregnancy. Studies in Finnish women indicated that heavy consumption of liquorice (equivalent to ≥ 500 mg/week of glycyrrhizic acid) during pregnancy was associated with an increased risk of preterm delivery.[1,2] Consumption of large amounts of liquorice was a social habit noted to occur in some northern European countries.

1. Strandberg TE, *et al.* Birth outcome in relation to licorice consumption during pregnancy. *Am J Epidemiol* 2001; **153:** 1085–8.
2. Strandberg TE, *et al.* Preterm birth and licorice consumption during pregnancy. *Am J Epidemiol* 2002; **156:** 803–5.

Uses and Administration

Liquorice is used as a flavouring and sweetening agent. It has demulcent and expectorant properties and has been used in cough preparations. It has ulcer-healing properties that may result from stimulation of mucus synthesis. It contains constituents that produce mineralocorticoid effects (see above). Liquorice may also possess some antispasmodic and laxative properties.

Deglycyrrhizinised liquorice has a reduced mineralocorticoid activity and has been used, usually with antacids, for the treatment of peptic ulcer disease (p.1702).

◊ Reviews.

1. Fiore C, *et al.* A history of the therapeutic use of liquorice in Europe. *J Ethnopharmacol* 2005; **99:** 317–24.

Preparations

Ph. Eur.: Liquorice Ethanolic Liquid Extract, Standardised;
USP 31: Licorice Fluidextract.

Proprietary Preparations (details are given in Part 3)
Braz.: Alcalergin; Brefus†; ***Cz.:*** Gallentee†; ***Fr.:*** Depiderm; Trio D†; ***Ger.:*** Fichtensirup N†; Lakriment Neu†; Suczulen mono†.

Multi-ingredient: numerous preparations are listed in Part 3.

Loperamide Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de loperamida; Loperamid Hidroklorür; Loperamid hydrochlorid; Lopéramide, chlorhydrate de; Loperamid-hidroklorid; Loperamidhydroklorid; Loperamidi hydrochloridum; Loperamidihydrokloridi; Loperamido hidrocloridas; R-18553. 4-(4-*p*-Chlorophenyl-4-hydroxypiperidino)-*NN*-dimethyl-2,2-diphenylbutyramide hydrochloride.

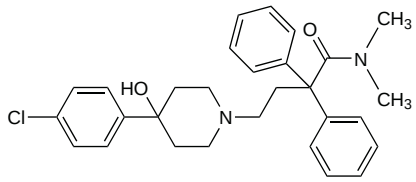
Лоперамида Гидрохлорид

$C_{29}H_{33}ClN_2O_2$,HCl = 513.5.

CAS — 53179-11-6 (loperamide); 34552-83-5 (loperamide hydrochloride).

ATC — A07DA03.

ATC Vet — QA07DA03.



(loperamide)

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

Ph. Eur. 6.2 (Loperamide Hydrochloride). A white or almost white powder. It exhibits polymorphism. Slightly soluble in water; freely soluble in alcohol and in methyl alcohol. Protect from light.

USP 31 (Loperamide Hydrochloride). A white to slightly yellow powder. Slightly soluble in water and in dilute acids; freely soluble in chloroform and in methyl alcohol; very slightly soluble in isopropyl alcohol.

Loperamide Oxide *(BAN, rINN)*

Loperamid oxid; Lopéramide Oxyde; Lopéramide, oxyde de; Loperamidi oxidum; Loperamidioksidi; Loperamido oksidas; Loperamidoxid; Loperamidum Oxidum; Óxido de loperamida; R-58425.

Лоперамида Оксид

$C_{29}H_{33}ClN_2O_3$ = 493.0.

CAS — 106900-12-3.

ATC — A07DA05.

ATC Vet — QA07DA05.

Pharmacopoeias. *Eur.* (see p.vii) includes the monohydrate.

Ph. Eur. 6.2 (Loperamide Oxide Monohydrate; Loperamidi Oxidum Monohydricum). A white or almost white, slightly hygroscopic, powder. Practically insoluble in water; freely soluble in alcohol and in dichloromethane. Store in airtight containers. Protect from light.

Adverse Effects and Treatment

Abdominal pain or bloating, nausea, constipation, dry mouth, dizziness, fatigue, and hypersensitivity reactions including skin rashes have been reported. Loperamide has been associated with paralytic ileus, particularly in infants and young children, and deaths have been reported. Depression of the CNS, to which children or those with hepatic impairment may be more sensitive, may be seen in overdosage; constipation and urinary retention also occur. Naloxone hydrochloride (see p.1454) has been recommended for treatment of severe overdosage.

Toxicity. Toxic megacolon has been reported[1,2] after use of loperamide. Severe effects reported in young children have included loss of consciousness[3,4] and delirium.[5] Several cases of paralytic ileus have also occurred in children,[6,7] some of which were fatal.[6]

1. Brown JW. Toxic megacolon associated with loperamide therapy. *JAMA* 1979; **241:** 501–2.
2. Walley T, Milson D. Loperamide related toxic megacolon in Clostridium difficile colitis. *Postgrad Med J* 1990; **66:** 582.
3. Minton NA, Smith PGD. Loperamide toxicity in a child after a single dose. *BMJ* 1987; **294:** 1383.
4. Chanzy S, *et al.* Perte de connaissance chez une jeune enfant secondaire à la prise de lopéramide. *Arch Pediatr* 2004; **11:** 826–7.
5. Schwartz RH, Rodriguez WJ. Toxic delirium possibly caused by loperamide. *J Pediatr* 1991; **118:** 656–7.
6. Bhutta TI, Tahir KI. Loperamide poisoning in children. *Lancet* 1990; **335:** 363.
7. Dudink J, *et al.* Ileus na gebruik van loperamide bij een kind met acute diarree. *Ned Tijdschr Geneeskd* 2003; **147:** 670–2.

Precautions

Loperamide should not be used when inhibition of peristalsis is to be avoided, in particular where ileus or constipation occur, and should be avoided in patients with abdominal distension, acute inflammatory bowel disease, or antibiotic-associated colitis. Loperamide should not be used alone in patients with dysentery.

Loperamide should be used with caution in patients with hepatic impairment because of its considerable first-pass metabolism in the liver. It should also be used with caution in young children because of a greater variability of response in this age group; it is not recommended for use in infants (see Uses and Administration, below).

Breast feeding. Loperamide is distributed into breast milk in small amounts.[1] The American Academy of Pediatrics[2] states that there have been no reports of any clinical effect on the infant associated with the use of loperamide by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding.

1. Nikodem VC, Hofmeyr GJ. Secretion of the antidiarrhoeal agent loperamide oxide in breast milk. *Eur J Clin Pharmacol* 1992; **42:** 695–6.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 18/01/06)

Interactions

Loperamide may increase the gastrointestinal absorption of desmopressin (p.2186).

Antifungals. A pharmacokinetic study in 12 healthy subjects found that *itraconazole* significantly increased peak plasma concentrations and area under the concentration-time curve of loperamide, and also prolonged the half-life of loperamide. Itraconazole also inhibited metabolism of loperamide to *N*-desmethylloperamide, suggesting that metabolism of loperamide in humans concurs with *in-vitro* data (see Metabolism, below). Use of itraconazole with gemfibrozil (see Cardiovascular Drugs, below) synergistically increased exposure to loperamide.[1]

1. Niemi M, *et al.* Itraconazole, gemfibrozil and their combination markedly raise the plasma concentrations of loperamide. *Eur J Clin Pharmacol* 2006; **62:** 463–72.

Antivirals. In a single-dose study,[1] oral *ritonavir* significantly increased the bioavailability of loperamide, possibly through inhibition of the cytochrome P450 isoenzyme CYP3A4, and not necessarily as originally supposed through P-glycoprotein inhibition. No serious adverse effects occurred. Licensed information for one UK preparation of loperamide (*Imodium; Janssen-Cilag, UK*) states that the clinical relevance of the pharmacokinetic interaction with P-glycoprotein inhibitors such as ritonavir is unknown.

For the effect of loperamide on *saquinavir*, and the corresponding effect of the antiviral on loperamide concentrations, see Gastrointestinal Drugs, under Interactions of Indinavir, p.884.

1. Tayrouz Y, *et al.* Ritonavir increases loperamide plasma concentrations without evidence for P-glycoprotein involvement. *Clin Pharmacol Ther* 2001; **70:** 405–14.

Cardiovascular drugs. A pharmacokinetic study in 12 healthy subjects found that *gemfibrozil* significantly increased peak plasma concentrations and area under the concentration-time curve of loperamide, and also prolonged the half-life of loperamide. Gemfibrozil also inhibited metabolism of loperamide to *N*-desmethylloperamide, suggesting that metabolism of loperamide in humans concurs with *in-vitro* data (see Metabolism, below). Use of gemfibrozil with itraconazole (see Antifungals, above) synergistically increased exposure to loperamide.[1]

1. Niemi M, *et al.* Itraconazole, gemfibrozil and their combination markedly raise the plasma concentrations of loperamide. *Eur J Clin Pharmacol* 2006; **62:** 463–72.

Co-trimoxazole. Use with co-trimoxazole increases the bioavailability of loperamide,[1] apparently by inhibiting its first-pass metabolism.

1. Kamali F, Huang ML. Increased systemic availability of loperamide after oral administration of loperamide and loperamide oxide with cotrimoxazole. *Br J Clin Pharmacol* 1996; **41:** 125–8.

Quinidine. A small study[1] found that giving quinidine with loperamide caused respiratory depression in 8 healthy subjects; when given with placebo, loperamide produced no respiratory depression. The authors supposed that inhibition of P-glycoprotein by quinidine had increased entry of loperamide into the CNS.

1. Sadeque AJM, *et al.* Increased drug delivery to the brain by P-glycoprotein inhibition. *Clin Pharmacol Ther* 2000; **68:** 231–7.

Pharmacokinetics

About 40% of a dose of loperamide is reported to be absorbed from the gastrointestinal tract to undergo first-pass metabolism in the liver and excretion in the faeces via the bile as inactive conjugate; there is slight urinary excretion. Little intact drug reaches the systemic circulation. The elimination half-life is reported to be about 10 hours.

Metabolism. Loperamide is metabolised to desmethylloperamide through *N*-demethylation. An *in-vitro* study established that this occurs mainly via cytochrome P450 isoenzymes CYP2C8 and CYP3A4; CYP2B6 and CYP2D6 also play a role. Loperamide is also a substrate of P-glycoprotein.[1]

1. Kim K-A, *et al.* Identification of cytochrome P450 isoforms involved in the metabolism of loperamide in human liver microsomes. *Eur J Clin Pharmacol* 2004; **60:** 575–81.

Uses and Administration

Loperamide is a synthetic derivative of pethidine that inhibits gut motility and may also reduce gastrointestinal secretions. It is given orally as an antidiarrhoeal drug as an adjunct in the management of acute and chronic diarrhoeas and may also be used in the man-