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.

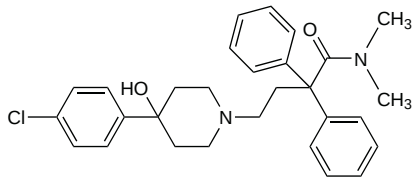
Лоперамида Гидрохлорид

$C_{29}H_{33}ClN_2O_2$,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-

agement of colostomies or ileostomies to reduce the volume of discharge.

In **acute diarrhoea** the usual initial dose for adults is loperamide hydrochloride 4 mg followed by 2 mg after each loose stool to a maximum of 16 mg daily; the usual daily dose is 6 to 8 mg. In the UK, it is not licensed for children under 4 years of age. Suggested doses for older children are: 4 to 8 years, 1 mg three or four times daily for up to 3 days; 9 to 12 years, 2 mg four times daily for up to 5 days. In the USA, loperamide is not recommended for children under the age of 2 years and an initial dose of 1 mg three times daily is suggested for children aged 2 to 5 years. (For restrictions on the use of loperamide in children and the view that antidiarrhoeal drugs should not be used at all in children, see Diarrhoea, below.)

In **chronic diarrhoea** the usual initial dose for adults is 4 to 8 mg daily in divided doses subsequently adjusted as necessary; doses of 16 mg daily should not be exceeded. If no improvement has been seen after treatment with 16 mg daily for at least 10 days, further use is unlikely to be of benefit. Although not licensed for use in children for chronic diarrhoea, in the UK the *BNFC* allows for the following oral doses of loperamide hydrochloride:

- 1 month to 1 year: 100 to 200 micrograms/kg twice daily, given 30 minutes before feeds; up to a maximum of 2 mg/kg daily in divided doses may be required
- 1 to 12 years: 100 to 200 micrograms/kg (maximum dose 2 mg) three to four times daily; up to 1.25 mg/kg daily in divided doses may be required, to a maximum of 16 mg daily
- 12 to 18 years: 2 to 4 mg two to four times daily, to a maximum of 16 mg daily

Loperamide is also given as the prodrug, **loperamide oxide**, which is converted to loperamide in the gastrointestinal tract. It has been given for acute diarrhoea in doses of 2 to 4 mg initially followed by 1 mg after each loose stool, to a maximum of 8 mg daily.

Diarrhoea. The mainstay of treatment for acute diarrhoea (p.1694) is rehydration therapy. Antidiarrhoeals may have a role for symptomatic relief in adults with acute diarrhoea, and loperamide is often chosen in such circumstances,[1] but WHO does not recommend the use of *any* antidiarrhoeal drug in children with diarrhoea. Similarly, in the UK the *BNFC* considers that antimotility drugs are not to be recommended for acute diarrhoea in children under 12 years of age. There have been problems regarding the use of antidiarrhoeals such as loperamide in young children in developing countries. Manufacturers have considered that a lower age limit is acceptable in those countries than is recommended in the UK or USA; even that lower limit is not always observed in practice and there have been reports of serious toxicity in very young children.[2] In response to such reports the manufacturers withdrew concentrated drops of loperamide worldwide and the syrup from countries where the WHO had a programme for control of diarrhoeal diseases,[3] but tablets and capsules remain available. In some countries the use of antidiarrhoeals is now restricted by law.

In the UK, NICE states that loperamide is the antidiarrhoeal of first choice in adults with faecal incontinence;[4] it can be used long-term in doses from 500 micrograms to 16 mg daily as needed. Loperamide should be started at a very low dose which can be increased as needed, and then adjusted in response to stool consistency. It should not be given to those with hard or infrequent stools, those with acute diarrhoea of unknown cause, or with acute ulcerative colitis. Patients who are unable to tolerate loperamide may be offered codeine phosphate (p.37) or co-phenotrope (see Diphenoxylate Hydrochloride, p.1724).

For mention of the use of loperamide in the management of diarrhoea caused by chemotherapy, see p.640.

1. Wingate D, *et al.* Guidelines for adults on self-medication for the treatment of acute diarrhoea. *Aliment Pharmacol Ther* 2001; **15:** 773–82.
2. Bhutta TI, Tahir KI. Loperamide poisoning in children. *Lancet* 1990; **335:** 363.
3. Gussin RZ. Withdrawal of loperamide drops. *Lancet* 1990; **335:** 1603–4.
4. NICE. Faecal incontinence: the management of faecal incontinence in adults (issued June 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/CG49NICEGuidance.pdf (accessed 31/03/08)

PRODRUG THERAPY. References to the use of *loperamide oxide* in diarrhoea.

1. Van Den Eynden B, *et al.* New approaches to the treatment of patients with acute, nonspecific diarrhea: a comparison of the effects of loperamide and loperamide oxide. *Curr Ther Res* 1995; **56:** 1132–41.
2. Hughes IW, *et al.* First-line treatment in acute non-dysenteric diarrhoea: clinical comparison of loperamide oxide, loperamide and placebo. *Br J Clin Pract* 1995; **49:** 181–5.
3. van Outryve M, Toussaint J. Loperamide oxide for the treatment of chronic diarrhoea in Crohn's disease. *J Int Med Res* 1995; **23:** 335–41.
4. Sun WM, *et al.* Effects of loperamide oxide on gastrointestinal transit time and anorectal function in patients with chronic diarrhoea and faecal incontinence. *Scand J Gastroenterol* 1997; **32:** 34–8.

Preparations

BP 2008: Loperamide Capsules;
USP 31: Loperamide Hydrochloride Capsules; Loperamide Hydrochloride Oral Solution; Loperamide Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Colifilm; Contem; Custey; Dotalsec; Elcoman; Ionet; Lansek A; Lefa Enteril L; Minicam; Plexol; Plorinoc; Regulane; Salvaxil†; Suprasec; Viltar; ***Austral.:*** Chemists Own Diarrhoea Relief; Gastro-Stop; Harmonise; Imodium; Neogastro†; ***Austria:*** Enterobene; Imodium; Lopedium; Normakut; ***Belg.:*** Imodium; ***Braz.:*** Diafuran; Diarresec†; Diasec†; Imosec; Loperin; Magnostase; ***Canad.:*** Anti-Diarrheal; Diahalt†; Diarr-Eze; Diarrhoea Relief; Imodium; Loperacap; ***Chile:*** Capent; Coliper; Lopediar; ***Cz.:*** Dissenten; Imodium; Loperon; ***Denm.:*** Dialope; Imodium; Propiden; Travello†; ***Fin.:*** Imocur; Imodium; Lopex†; ***Fr.:*** Altocel†; Arestal; Diaretyl; Dyspagon; Ercestop; Imodium; Imodiumlingual; Imossel; Indiaral; Nabutil†; ***Ger.:*** Azuperamid†; Boxolip; duralopid; Endialop; Endiaron†; Imodium; Lop-Dia; Lopalind; Lopedium; Lopepham†; Lopera akut†; Loperhoe; ***Gr.:*** Imodium; Neo-Enteroseptol; ***Hong Kong:*** Colodium†; Diatabs Reformulated; Imodium; Imodonl; Loper; Loperamil; Loperax; Loperium; Lopermide†; Mar-Loper; Reximide; Synodium; Vacontil†; Vidaperamide; ***Hung.:*** Enterobene; Imodium; Lopedium; Loperacap; ***India:*** Diarlop; Lopamide; Roko; ***Indon.:*** Alphamid; Amerol; Antidia; Colidium; Diadium; Diasec; Imodium; Imomed; Imore; Imosa; Inamid; Lexadium; Lodia; Loremid; Motilex; Normotil; Normudal; Opox; Oramide; Primodium; Renamid; Xepare; Zeroform; ***Irl.:*** Arret; Diarrest RF; Imodium; ***Israel:*** Imodium; Loperid; Loperium; Rekamide; Shilshul X; Stopit; ***Ital.:*** Diarstop; Diarzero; Dissenten; Imodium; Lopemid; Ramidox†; Tebloc†; ***Malaysia:*** Beamodium; Diatrol†; Imocap†; Imodium; Imotab†; Loperax†; Lopenium; Lopermide; Loramide; Miraton†; Vacontil; ***Mex.:*** Acanol; Acqta; Apo-Pera; Biolid†; Cryoperacid; Deroser; Dialacid†; Diaperol; Dilostop†; Exclefin; F9†; Hurplex; Imodium; Lomotil; Lop; Nodiamex; Permidal; Pramidal; Raxamida†; Rediarin; Top-Dal; Valfam; ***Neth.:*** Arestal; Diacure; Diarem; Imodium; Kruidvat Diarreeremmer; Trekpleister Diarreeremmer†; ***Norw.:*** Imodium; Travello; ***NZ:*** Diamide; Dicap; Imodium; Nodia; ***Philipp.:*** Diamide; Diaperyl; Diatabs (Reformulated); Imodium; Lormide; Tymedon; ***Pol.:*** Imodium; Laremid; Stoperan; ***Port.:*** Dyspagon; Fulcalrex; Imodium; Loprex; Loride; ***Rus.:*** Imodium (*Имодиум*); Lopedium (*Лопедиум*); ***S.Afr.:*** Betaperamide; Gastron; Imodium; Lenide-T; Lopedium; Loperastat; Norimode; Prodium; ***Singapore:*** Colodium†; IMD†; Imodium; Loperamil; Lopermide; Loramide†; Lorpa; Vacontil; ***Spain:*** Elissan; Fortasec; Imodium; Imosec†; Loperan; Loperkey; Protector; Salvacolina; Taguinol; ***Swed.:*** Dimor; Imodium; Primodium; Travello; ***Switz.:*** Binaldan; Imodium; Lopimed; Zorotop; ***Thai.:*** Diarent; Diarodil; Entermid; Imodium; Impelium; Lomide; Lomy†; Lopaminе†; Lopela; Lopercin; Loperdium; Loperia; Lopermide; Operium†; Perasian; SBOB†; ***Turk.:*** Diadef; Lopermid; ***UK:*** Arret; Diah-Limit; Diaquitte; Diareze; Diocalm Ultra; Diocaps; Entrocalm; Imodium; Norimode; Normaloe; ***USA:*** Imodium; K-Pek II; Kao-Paverin; Kaopectate II†; Neo-Diaral; Pepto Diarrhea Control; ***Venez.:*** Glucitol; Imodium; Loperam; Mentaden†; Oldan†; Polonit†.

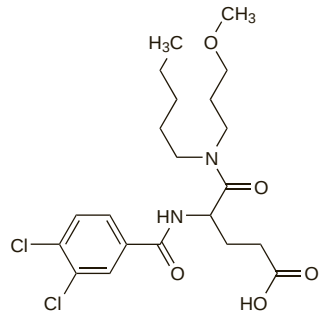
Multi-ingredient: ***Arg.:*** Neo Kef; Neomas L; Regulane AF; ***Austral.:*** Imodium Advanced; ***Austria:*** Imodium Plus; ***Belg.:*** Imodium Plus; ***Braz.:*** Imodium Plus†; ***Canad.:*** Imodium Advanced; ***Cz.:*** Imodium Plus; ***Denm.:*** Imodium med Simethicon; ***Fr.:*** Imodiumduo; ***Ger.:*** Imodium Plus; ***Hong Kong:*** Imodium Plus; ***Hung.:*** Imodium Komplett†; ***Mex.:*** Imodium Plus; ***NZ:*** Imodium Advanced; ***Pol.:*** Imodium Plus; ***Port.:*** Imodium Plus; ***S.Afr.:*** Imodium Plus; ***Spain:*** Imodium Plus; ***Switz.:*** Imodium Plus; ***Thai.:*** Imodium Plus; ***UK:*** Imodium Plus; ***USA:*** Imodium Advanced.

Loxiglumide *(rINN)*

CR-1505; CR-2017 (dexloxiglumide); Loxiglumida; Loxiglumidum. (±)-4-(3,4-Dichlorobenzamido)-*N*-(3-methoxypropyl)-*N*-pentylglutaramic acid.

Локсиглумид

$C_{21}H_{30}Cl_2N_2O_5$ = 461.4.
CAS — 107097-80-3 (loxiglumide); 119817-90-2 (dexloxiglumide).



Profile

Loxiglumide is a specific cholecystokinin antagonist related to proglumide (see p.1764), and has been investigated in biliary and gastrointestinal dyskinesias, constipation and irritable bowel syndrome, and pancreatitis.

The *R*-isomer of loxiglumide, dexloxiglumide is also under investigation for constipation-predominant irritable bowel syndrome.

◊ References.

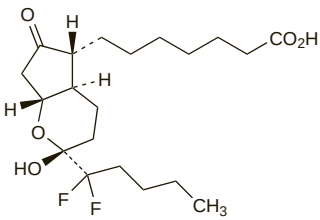
1. Shiratori K, *et al.* Clinical evaluation of oral administration of a cholecystokinin-A receptor antagonist (loxiglumide) to patients with acute, painful attacks of chronic pancreatitis: a multicenter dose-response study in Japan. *Pancreas* 2002; **25:** e1–e5.
2. Cremonini F, *et al.* Effect of CCK-1 antagonist, dexloxiglumide, in female patients with irritable bowel syndrome: a pharmacodynamic and pharmacogenomic study. *Am J Gastroenterol* 2005; **100:** 652–63.
3. Persiani S, *et al.* Pharmacokinetic profile of dexloxiglumide. *Clin Pharmacokinet* 2006; **45:** 1177–88.

Lubiprostone *(USAN, rINN)*

Lubiprostona; Lubiprostonum; RU-0211; SPI-0211. (–)-7-[(2*R*,4a*R*,5*R*,7a*R*)-2-(1,1-Difluoropentyl)-2-hydroxy-6-oxooctahydrocyclopenta[*b*]pyran-5-yl]heptanoic acid.

Лубипростон

$C_{20}H_{32}F_2O_5$ = 390.5.
CAS — 136790-76-6; 333963-40-9.



Adverse Effects and Precautions

The most common adverse effect of lubiprostone is nausea, which is dose-dependent and may be severe in some patients. Symptoms can be reduced by taking lubiprostone with food. Diarrhoea also occurs commonly, and other gastrointestinal effects include abdominal distension and pain, flatulence, and vomiting. Other reported adverse effects include headache, dizziness, fatigue, dyspnoea, and peripheral oedema. Chest discomfort, back pain, and arthralgia can occur.

Lubiprostone is contra-indicated in patients with a history of mechanical gastrointestinal obstruction.

Pharmacokinetics

A negligible amount of lubiprostone is absorbed systemically after an oral dose. It is rapidly and extensively metabolised by carbonyl reductase, probably in the stomach and jejunum.

Uses and Administration

Lubiprostone is a chloride-channel activator that acts locally in the gut to increase intestinal fluid secretion, which increases motility. It is used in the treatment of chronic idiopathic constipation (p.1693) in a dose of 24 micrograms twice daily, taken orally with food. It is also under investigation in the treatment of constipation-predominant irritable bowel syndrome.

◊ References.

1. McKeage K, *et al.* Lubiprostone. *Drugs* 2006; **66:** 873–9.
2. Anonymous. Lubiprostone (Amitiza) for chronic constipation. *Med Lett Drugs Ther* 2006; **48:** 47–8.
3. Ambizas EM, Ginzburg R. Lubiprostone: a chloride channel activator for treatment of chronic constipation. *Ann Pharmacother* 2007; **41:** 957–64.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Amitiza.

Magaldrate *(BAN, USAN, rINN)*

Aluminum Magnesium Hydroxide Sulfate; AY-5710; Magaldraatti; Magaldrát; Magaldrat; Magaldratas; Magaldrato; Magaldratum.

Магальдрат

$Al_5Mg_{10}(OH)_{31}(SO_4)_2,xH_2O$ = 1097.3 (anhydrous).
CAS — 74978-16-8.
ATC — A02AD02.
ATC Vet — QA02AD02.

NOTE. Magaldrate was formerly described as Aluminium Magnesium Hydroxide ($AlMg_2(OH)_7$ monohydrate, *CAS—1317-26-6*).

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

Ph. Eur. 6.2 (Magaldrate). A combination of aluminium and magnesium hydroxides (see p.1706 and p.1743 respectively) and sulfates. It contains the equivalent of 90 to 105% of $Al_5Mg_{10}(OH)_{31}(SO_4)_2$, calculated with reference to the dried substance. A white or almost white crystalline powder. Practically insoluble in water and in alcohol; soluble in dilute mineral acids. It loses between 10 and 20% of its weight on drying at 200° for 4 hours.

USP 31 (Magaldrate). A combination of aluminium and magnesium hydroxides and sulfates. It contains the equivalent of 90 to