Administration in children. In the UK, children may be given the following oral doses of lactulose 3.35 g per 5 mL solution for constipation; doses may be adjusted according to response:

- 1 month to 1 year: 2.5 mL twice daily
- 1 to 5 years: 5 mL twice daily
- 5 to 10 years: 10 mL twice daily
- 10 to 18 years: 15 mL twice daily

Diagnosis and testing. ***THE SUGAR ABSORPTION TEST.*** In healthy individuals lactulose is largely unabsorbed from the gastrointestinal tract, but in, for example, coeliac disease there is increased permeability to disaccharides such as lactulose and a paradoxical decrease in the absorption of monosaccharides. This led to the development of the differential sugar absorption test in which 2 sugars are given simultaneously by mouth and the urinary recovery of each is determined; mannitol is commonly used as the monosaccharide component and lactulose as the disaccharide. Alternatives include mannitol plus cellobiose and rhamnose plus lactulose. This absorption test is useful in the investigation of intestinal disease.[1]

The lack of a standardised test solution has hampered comparison of test results. Although hyperosmolar solutions are better at determining intestinal damage,[2] some have preferred to use low osmolar solutions because of the risk of inducing osmotic diarrhoea, especially in children.

A study found the sugar absorption test to be strongly predictive of an organic cause of chronic diarrhoea; it may be useful in improving the selection of patients who need further evaluation.[3]

THE LACTOSE BREATH TEST (hydrogen breath test). Lactulose is converted by bacteria in the large bowel to short chain fatty acids with the production of small quantities of hydrogen gas. The hydrogen is rapidly absorbed and is exhaled in the breath and measurement of its production is used to measure orocaecal transit time and carbohydrate malabsorption. However, even small doses of lactulose shortens transit time, which may limit the value of this test.[4]

The test is also diagnostic for bacterial overgrowth in the small intestine, which is increased in irritable bowel syndrome. Although hydrogen is produced in most subjects, methane is also produced in up to 50% of healthy subjects, and data suggest there may be clinical implications to different gas profiles. A study found that the presence of methane was associated with constipation, and with constipation-predominant irritable bowel syndrome. Methane production was infrequent in diarrhoea-predominant irritable bowel syndrome and virtually absent in inflammatory bowel disease. Diarrhoea and inflammatory bowel disease were associated with hydrogen production. Whether the type of bacterial flora causally determines symptoms is as yet unknown.[5]

1. Uil JJ, *et al.* Clinical implications of the sugar absorption test: intestinal permeability test to assess mucosal barrier function. *Scand J Gastroenterol* 1997; **223** (suppl): 70–8.
2. Uil JJ, *et al.* Sensitivity of a hyperosmolar or "low"-osmolar test solution for sugar absorption in recognizing small intestinal mucosal damage in coeliac disease. *Dig Liver Dis* 2000; **32:** 195–200.
3. Di Leo V, *et al.* Lactulose/mannitol test has high efficacy for excluding organic causes of chronic diarrhea. *Am J Gastroenterol* 2003; **98:** 2245–52.
4. Miller MA, *et al.* Comparison of scintigraphy and lactulose breath hydrogen test for assessment of orocecal transit: lactulose accelerates small bowel transit. *Dig Dis Sci* 1997; **42:** 10–18.
5. Pimentel M, *et al.* Methane production during lactulose breath test is associated with gastrointestinal disease presentation. *Dig Dis Sci* 2003; **48:** 86–92.

Preparations

BP 2008: Lactulose Oral Powder;
Ph. Eur.: Liquid Lactulose;
USP 31: Lactulose Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Genocolan; Lactulon; Lafelax; Medixin; Tenualax; ***Austral.:*** Actilax; Duphalac; Genlac; Lac-Dol; Lactocur; ***Austria:*** Bifiteral; Duphalac; Laevolac; ***Belg.:*** Bifiteral; Certalac†; Duphalac; ***Braz.:*** Colonac; Farlac; Lactulona; Pentalac†; ***Canad.:*** Acilac†; Gen-Lac; Laxilose†; ***Chile:*** Axant; Dismam; Duphalac; Rencef†; ***Cz.:*** Duphalac; Lactecon; Laevolac†; ***Denm.:*** Danilax†; Medilax; ***Fin.:*** Duphalac; Levolac; Loraga†; ***Fr.:*** Duphalac; Laxaron; ***Ger.:*** Bifinorma; Bifiteral; Eugalac; Hepa-Merz Lact†; Hepaticum-Lac-Medice†; Kattwilact†; Lactocur; Lactuflor; Lactuverlan; Laevilac S; Medilet†; Tulotract; ***Gr.:*** Duphalac; Purgolac†; ***Hong Kong:*** Danilax; Duphalac; Laevolac; Martulose; ***Hung.:*** Duphalac; Laevolac; ***India:*** Duphalac; Livoluk; ***Indon.:*** Constipen; Dulcolactol; Duphalac; Lactulax; Lantulos; Laxadilac; Opilax; Pralax; Solac; ***Irl.:*** Dulax; Duphalac; Gerelax; Laxose; ***Israel:*** Avilac; Gerelax; Lactulax; Laevolac; ***Ital.:*** Biolac†; Dia-Colon; Duphalac; Epalat EPS; Epalfen; Lactoger†; Laevolac; Lassifar†; Lattubio†; Lattulac; Lis†; Normase; Osmolac†; Sintolatt; Verelait; ***Jpn:*** Monilac; ***Malaysia:*** Dhactulose; Duphalac; Lactul; Lactumed†; ***Mex.:*** Lactulax; Regulact; ***Neth.:*** Duphalac; Epalfen; Laxeersiroop; Legendal; ***Norw.:*** Duphalac; Levolac; ***NZ:*** Laevolac; ***Philipp.:*** Duphalac; Lilac; ***Pol.:*** Duphalac; Lactulol; Normalac; Normase; ***Port.:*** Colsanac; Duphalac; Lactecon†; Laevolac; Obstipar; ***Rus.:*** Duphalac (Дюфалак); Normase (Нормазе); Portalac (Порталак); ***S.Afr.:*** Adco-Liquilax; Duphalac; Lacson; Laxette; ***Singapore:*** Dhactulose; Duphalac; Lactus; ***Spain:*** Belmalax; Duphalac; ***Swed.:*** Duphalac; Laktipex; Loraga; ***Switz.:*** Duphalac; Gatinar; Legendal; Rudolac; ***Thai.:*** Duphalac; Hepalac; Laevolac†; ***Turk.:*** Duphalac; Lactulac; Laevolac; Laktol; Osmolak; ***UAE:*** Soflax; ***UK:*** Duphalac; Lactugal; Lemlax; Regulose; ***USA:*** Cephulac; Cholac†; Chronulac; Constilac; Constulose; Duphalac; Enulose; Kristalose; ***Venez.:*** Lactulona; Moderan.

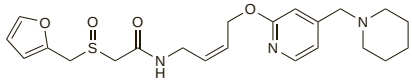
Multi-ingredient: ***Arg.:*** Bifidosa; ***Fr.:*** Melaxose; Transulose; ***Ger.:*** Eugalan Topfer; ***Indon.:*** Laktobion; ***Ital.:*** Combilax; Lactolas; Lactomannan; Levoplus; Naturalass; ***Neth.:*** Transulose; ***Port.:*** Melaxose.

Lafutidine *(rINN)*

FRG-8813; Lafutidina; Lafutidinum. (±)-2-(Furfurylsulfinyl)-*N*-[(*Z*)-4-{[4-(piperidinomethyl)-2-pyridyl]oxy}-2-butenyl]acetamide.

Лафутидин

$C_{22}H_{29}N_3O_4S$ = 431.5.
CAS — 118288-08-7.
ATC — A02BA08.
ATC Vet — QA02BA08.



Profile

Lafutidine, like cimetidine (p.1716), is a histamine H_2-antagonist. It is used in the management of peptic ulcer disease.

◊ References.
1. Uesugi T, *et al.* The efficacy of lafutidine in improving preoperative gastric fluid property: a comparison with ranitidine and rabeprazole. *Anesth Analg* 2002; **95:** 144–7.
2. Mikawa K, *et al.* Lafutidine vs cimetidine to decrease gastric fluid acidity and volume in children. *Can J Anaesth* 2003; **50:** 425–6.
3. Isomoto H, *et al.* Lafutidine, a novel histamine H2-receptor antagonist, vs lansoprazole in combination with amoxicillin and clarithromycin for eradication of Helicobacter pylori. *Helicobacter* 2003; **8:** 111–19.
4. Inamori M, *et al.* Early effects of lafutidine or rabeprazole on intragastric acidity: which drug is more suitable for on-demand use? *J Gastroenterol* 2005; **40:** 453–8.
5. Higuchi K, *et al.* Lafutidine can improve the quality of gastric ulcer healing in humans: a randomized, controlled, multicenter trial. *Inflammopharmacology* 2006; **14:** 226–30.
6. Yamagishi H, *et al.* Stronger inhibition of gastric acid secretion by lafutidine, a novel H(2) receptor antagonist, than by the proton pump inhibitor lansoprazole. *World J Gastroenterol* 2008; **14:** 2406–10.

Preparations

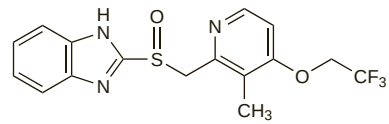
Proprietary Preparations (details are given in Part 3)
Jpn: Protecadin; Stogar.

Lansoprazole *(BAN, USAN, rINN)*

A-65006; AG-1749; Lansopratsoli; Lansoprazol; Lansoprazolum. 2-({3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methyl} sulphinylbenzimidazole.

Лансопразол

$C_{16}H_{14}F_3N_3O_2S$ = 369.4.
CAS — 103577-45-3.
ATC — A02BC03.
ATC Vet — QA02BC03.



Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Lansoprazole). A white or brownish powder. Practically insoluble in water; soluble in anhydrous alcohol; very slightly soluble in acetonitrile. It exhibits polymorphism. Store in airtight containers. Protect from light.
USP 31 (Lansoprazole). A white to brownish-white powder. Practically insoluble in water; freely soluble in dimethylformamide. Store in airtight containers at a temperature not exceeding 40°. Protect from light.

Adverse Effects and Precautions

As for Omeprazole, p.1753.

◊ Reviews.
1. Freston JW, *et al.* Safety profile of lansoprazole: the US clinical trial experience. *Drug Safety* 1999; **20:** 195–205.

Effects on the blood. For a report of thrombocytopenia with lansoprazole, see under Omeprazole, p.1753.

Effects on the endocrine system. For cases of gynaecomastia associated with lansoprazole, see p.1753.

Effects on the gastrointestinal tract. Glossitis (associated in some cases with black tongue or stomatitis) has been reported in a few patients taking lansoprazole as part of a triple therapy regimen for *Helicobacter pylori* elimination in peptic ulcer disease.[1] Discoloured tongue has been reported in a patient taking lansoprazole alone.[2]

An increase in gastritis occurred in patients infected with *Helicobacter pylori* when given long-term lansoprazole therapy.[3] For further discussion of the link between *H. pylori*, gastritis, and proton pump inhibitor use, see Gastrointestinal Tumours, p.1754.

For a suggestion that the incidence of diarrhoea may be greater with lansoprazole than omeprazole see Incidence of Adverse Effects, p.1753. Cases of microscopic colitis have been reported with use of lansoprazole.[4] UK licensed product information states that stopping therapy should be considered in the case of severe and/or persistent diarrhoea.

1. Greco S, *et al.* Glossitis, stomatitis, and black tongue with lansoprazole plus clarithromycin and other antibiotics. *Ann Pharmacother* 1997; **31:** 1548.
2. Scully C. Discoloured tongue: a new cause? *Br J Dermatol* 2001; **144:** 1293–4.
3. Berstad AE, *et al.* Helicobacter pylori gastritis and epithelial cell proliferation in patients with reflux oesophagitis after treatment with lansoprazole. *Gut* 1997; **41:** 740–7.
4. Hilmer SN, *et al.* Microscopic colitis associated with exposure to lansoprazole. *Med J Aust* 2006; **184:** 185–6.

Effects on the musculoskeletal system. For reference to a case of eosinophilia and myalgia related to lansoprazole therapy, see p.1753.

Effects on the skin. For mention of skin reactions to lansoprazole, see p.1754.

Interactions

As for Omeprazole, p.1755. Antacids and sucralfate may reduce the bioavailability of lansoprazole, and should not be taken within 1 hour of a dose of lansoprazole.

◊ For reference to a lack of effect of lansoprazole on diazepam, see Gastrointestinal Drugs, p.991, and for a clinically insignificant effect on theophylline clearance, see p.1145. For reference to glossitis occurring when lansoprazole was used with some antibacterials, see Effects on the Gastrointestinal Tract, above.

Pharmacokinetics

Lansoprazole is rapidly absorbed after oral doses, with peak plasma concentrations achieved after about 1.5 to 2 hours. Bioavailability is reported to be 80% or more even with the first dose, although the drug must be given in an enteric-coated form since lansoprazole is unstable at acid pH. Food slows the absorption of lansoprazole and reduces the bioavailability by about 50%. It is extensively metabolised in the liver, primarily by cytochrome P450 isoenzyme CYP2C19 to form 5-hydroxyl-lansoprazole and by CYP3A4 to form lansoprazole sulfone. Metabolites are excreted mainly in faeces via the bile; only about 15 to 30% of a dose is excreted in urine. The plasma elimination half-life is around 1 to 2 hours but the duration of action is much longer. Lansoprazole is about 97% bound to plasma protein. Clearance is decreased in elderly patients, and in hepatic impairment.

◊ References.
1. Hussein Z, *et al.* Age-related differences in the pharmacokinetics and pharmacodynamics of lansoprazole. *Br J Clin Pharmacol* 1993; **36:** 391–8.
2. Flouvat B, *et al.* Single and multiple dose pharmacokinetics of lansoprazole in elderly subjects. *Br J Clin Pharmacol* 1993; **36:** 467–9.
3. Delhotal-Landes B, *et al.* Pharmacokinetics of lansoprazole in patients with renal or liver disease of varying severity. *Eur J Clin Pharmacol* 1993; **45:** 367–71.
4. Delhotal Landes B, *et al.* Clinical pharmacokinetics of lansoprazole. *Clin Pharmacokinet* 1995; **28:** 458–70.
5. Karol MD, *et al.* Lansoprazole pharmacokinetics in subjects with various degrees of kidney function. *Clin Pharmacol Ther* 1997; **61:** 450–8.
6. Tran A, *et al.* Pharmacokinetic-pharmacodynamic study of oral lansoprazole in children. *Clin Pharmacol Ther* 2002; **71:** 359–67.

Metabolism. As for omeprazole (p.1755), the cytochrome P450 isoenzyme CYP2C19 (*S*-mephenytoin hydroxylase) is involved in the hydroxylation of lansoprazole, and individuals who are deficient in this enzyme are poor metabolisers of lansoprazole.[1,2] There is some suggestion that the effect of this genetic polymorphism on lansoprazole may be less than the effect on omeprazole.[3]

1. Pearce RE, *et al.* Identification of the human P450 enzymes involved in lansoprazole metabolism. *J Pharmacol Exp Ther* 1996; **277:** 805–16.
2. Sohn DR, *et al.* Metabolic disposition of lansoprazole in relation to the S-mephenytoin 4′-hydroxylation phenotype status. *Clin Pharmacol Ther* 1997; **61:** 574–82.
3. Kim K-A, *et al.* Enantioselective disposition of lansoprazole in extensive and poor metabolizers of CYP2C19. *Clin Pharmacol Ther* 2002; **72:** 90–9.

Uses and Administration

Lansoprazole is a proton pump inhibitor with actions and uses similar to those of omeprazole (p.1755). It is used in the treatment of peptic ulcer disease and in oth-