Ranitidine *(BAN, USAN, rINN)*

AH-19065; Ranitidiini; Ranitidin; Ranitidina; Ranitidinum. *NN*-Dimethyl-5-[2-(1-methylamino-2-nitrovinylamino)ethylthiomethyl]furfurylamine.

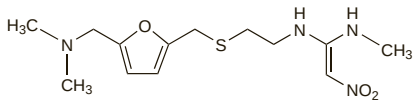
Ранитидин

$C_{13}H_{22}N_4O_3S$ = 314.4.

CAS — 66357-35-5.

ATC — A02BA02.

ATC Vet — QA02BA02.



Ranitidine Hydrochloride *(BANM, rINNM)*

AH-19065; Hidrocloruro de ranitidina; Ranitidiinihydrokloridi; Ranitidin Hidroklorür; Ranitidine, chlorhydrate de; Ranitidin-hidroklorid; Ranitidin-hydrochlorid; Ranitidinhydroklorid; Ranitidini hydrochloridum; Ranitidino hidrochloridas; Ranitydyny chlorowodorek.

Ранитидина Гидрохлорид

$C_{13}H_{22}N_4O_3S,HCl$ = 350.9.

CAS — 66357-59-3.

ATC — A02BA02.

ATC Vet — QA02BA02.

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

Ph. Eur. 6.2 (Ranitidine Hydrochloride). A white or pale yellow, crystalline powder. It exhibits polymorphism. Freely soluble in water; sparingly soluble or slightly soluble in dehydrated alcohol; very slightly soluble in dichloromethane. A 1% solution in water has a pH of 4.5 to 6.0. Store in airtight containers. Protect from light.

USP 31 (Ranitidine Hydrochloride). A white to pale yellow, practically odourless, crystalline powder. It is sensitive to light and to moisture. Very soluble in water; sparingly soluble in alcohol. A 1% solution in water has a pH of 4.5 to 6.0. Store in airtight containers. Protect from light.

Stability and incompatibility. References.

1. Chilvers MR, Lysne JM. Visual compatibility of ranitidine hydrochloride with commonly used critical-care medications. *Am J Hosp Pharm* 1989; **46:** 2057–8.
2. Wohlford JG, *et al.* More information on the visual compatibility of hetastarch with injectable critical-care drugs. *Am J Hosp Pharm* 1990; **47:** 297–8.
3. Williams MF, *et al.* In vitro evaluation of the stability of ranitidine hydrochloride in total parenteral nutrition mixtures. *Am J Hosp Pharm* 1990; **47:** 1574–9.
4. Galante LJ, *et al.* Stability of ranitidine hydrochloride at dilute concentration in intravenous infusion fluids at room temperature. *Am J Hosp Pharm* 1990; **47:** 1580–4.
5. Galante LJ, *et al.* Stability of ranitidine hydrochloride with eight medications in intravenous admixtures. *Am J Hosp Pharm* 1990; **47:** 1606–10.
6. Stewart JT, *et al.* Stability of ranitidine in intravenous admixtures stored frozen, refrigerated, and at room temperature. *Am J Hosp Pharm* 1990; **47:** 2043–6.
7. Montoro JB, Pou L. Comment on stability of ranitidine hydrochloride in total nutrient admixtures. *Am J Hosp Pharm* 1991; **48:** 2384.
8. Stewart JT, *et al.* Stability of ranitidine hydrochloride and seven medications. *Am J Hosp Pharm* 1994; **51:** 1802–7.
9. Crowther RS, *et al.* In vitro stability of ranitidine hydrochloride in enteral nutrient formulas. *Ann Pharmacother* 1995; **29:** 859–62.

Adverse Effects

As for Cimetidine, p.1716. Unlike cimetidine, ranitidine has little or no anti-androgenic effect, despite isolated reports of gynaecomastia and impotence.

◊ General references.

1. Wormsley KG. Safety profile of ranitidine: a review. *Drugs* 1993; **46:** 976–85.

Carcinogenicity. For a discussion of the possible association between histamine H_2-antagonists and cancer, including mention of a study with ranitidine, see Cimetidine, p.1717.

Effects on the blood. For a discussion of the adverse haematological effects of H_2-antagonists, see Cimetidine, p.1717.

Effects on the cardiovascular system. Similarly to cimetidine (p.1717), bradycardia,[1,2] AV block,[2] and cardiac arrest[3] have been reported rarely during ranitidine therapy. A positive inotropic effect, without significant changes in heart rate or blood pressure, has also been reported in healthy subjects[4] and pretreatment with ranitidine has blocked the cardiac depressant effects seen in some subjects given famotidine or nizatidine.[5] Although studies in critically ill patients[6] and healthy subjects[7,8] have found no adverse haemodynamic effects associated with ranitidine, it is likely that a small proportion of patients are more susceptible to the cardiovascular effects of ranitidine. Caution is recommended when ranitidine is given intravenously, particularly in patients with cardiovascular disease.

1. Johnson WS, Miller DR. Ranitidine and bradycardia. *Ann Intern Med* 1988; **108:** 493.
2. Tanner LA, Arrowsmith JB. Bradycardia and H antagonists. *Ann Intern Med* 1988; **109:** 434–5.
3. Hart AM. Cardiac arrest associated with ranitidine. *BMJ* 1989; **299:** 519.
4. Meyer EC, *et al.* Inotropic effects of ranitidine. *Eur J Clin Pharmacol* 1990; **39:** 301–3.
5. Mescheder A, *et al.* Changes in the effects of nizatidine and famotidine on cardiac performance after pretreatment with ranitidine. *Eur J Clin Pharmacol* 1993; **45:** 151–6.
6. Vohra SB, *et al.* The haemodynamic effects of ranitidine injected centrally in optimally resuscitated patients. *Br J Hosp Med* 1989; **42:** 149.
7. Hughes DG, *et al.* Cardiovascular effects of H -receptor antagonists. *J Clin Pharmacol* 1989; **29:** 472–7.
8. Hilleman DE, *et al.* Impact of chronic oral H -antagonist therapy on left ventricular systolic function and exercise capacity. *J Clin Pharmacol* 1992; **32:** 1033–7.

Effects on the endocrine system. Unlike cimetidine (p.1717), ranitidine does not bind to androgen receptors and has little, if any, anti-androgenic effect. Studies in men taking ranitidine for the management of duodenal ulcer[1,2] reported no significant changes in the plasma concentrations of testosterone, luteinising hormone, follicle-stimulating hormone, or prolactin after up to 2 years of treatment; no significant changes in sperm concentration, motility, or morphology were noted.[1] There have been isolated reports of gynaecomastia,[3] loss of libido,[4] and impotence[5] associated with ranitidine, but in 9 patients with cimetidine-induced breast changes and impotence, transfer to ranitidine resulted in resolution of these symptoms.[6]

1. Wang C, *et al.* Ranitidine does not affect gonadal function in man. *Br J Clin Pharmacol* 1983; **16:** 430–2.
2. Knigge U, *et al.* Plasma concentrations of pituitary and peripheral hormones during ranitidine treatment for two years in men with duodenal ulcer. *Eur J Clin Pharmacol* 1989; **37:** 305–7.
3. Tosi S, Cagnoli M. Painful gynaecomastia with ranitidine. *Lancet* 1982; **i:** 160.
4. Smith RN, Elsdon-Dew RW. Alleged impotence with ranitidine. *Lancet* 1983; **ii:** 798.
5. Kassianos GC. Impotence and nizatidine. *Lancet* 1989; **i:** 963.
6. Jensen RT, *et al.* Cimetidine-induced impotence and breast changes in patients with gastric hypersecretory states. *N Engl J Med* 1983; **308:** 883–7.

Effects on the eyes. For a report of an increase in intra-ocular pressure associated with ranitidine, see under Cimetidine, p.1717. A cohort study involving 140 128 patients receiving anti-ulcer therapy, 70 389 of whom received ranitidine, found no evidence that any of the drugs studied were associated with a major increased risk of vascular or inflammatory disorders of the eye.[1]

For reference to loss of colour vision in a child receiving ranitidine see under Effects on the Nervous System, below.

1. García Rodríguez LA, *et al.* A cohort study of the ocular safety of anti-ulcer drugs. *Br J Clin Pharmacol* 1996; **42:** 213–16.

Effects on the kidneys. For reference to interstitial nephritis associated with H_2-antagonists including ranitidine, see under Cimetidine, p.1717.

Effects on the liver. There have been some case reports of ranitidine hepatotoxicity.[1-3] The increase in relative risk seen in a large cohort study involving 108 891 patients receiving antisecretory therapy was less for ranitidine (1.7:1) than for cimetidine (see p.1717).

1. Souza Lima MA. Ranitidine and hepatic injury. *Ann Intern Med* 1986; **105:** 140.
2. Ramrakhiani S, *et al.* Possible cholestatic injury from ranitidine with a review of the literature. *Am J Gastroenterol* 1998; **93:** 822–6.
3. Liberopoulos EN, *et al.* Possible ranitidine-induced cholestatic jaundice. *Ann Pharmacother* 2002; **36:** 172.

Effects on the nervous system. Ranitidine has been associated with adverse neurological effects including confusion,[1-8] loss of colour vision,[4] aggressiveness,[2,4,6] lethargy,[8] somnolence,[8] disorientation,[8] depression,[8] hallucinations,[1,7-9] and severe headache.[10] As with cimetidine (p.1717) these reactions occur mainly in the elderly, the severely ill, or patients with renal or hepatic impairment. Single-dose studies in young healthy subjects have found no adverse changes in performance, CNS function, or subjective assessment of mood after oral doses of ranitidine 150 or 300 mg.[11]

1. Hughes JD, *et al.* Mental confusion associated with ranitidine. *Med J Aust* 1983; **2:** 12–13.
2. Silverstone PH. Ranitidine and confusion. *Lancet* 1984; **i:** 1071.
3. Epstein CM. Ranitidine and confusion. *Lancet* 1984; **i:** 1071.
4. De Giacomo C, *et al.* Ranitidine and loss of colour vision in a child. *Lancet* 1984; **ii:** 47.
5. Mani RB, *et al.* H -receptor blockers and mental confusion. *Lancet* 1984; **ii:** 98.
6. Mandal SK. Psychiatric side effects of ranitidine. *Br J Clin Pract* 1986; **40:** 260.
7. MacDermott AJ, *et al.* Acute confusional episodes during treatment with ranitidine. *BMJ* 1987; **294:** 1616.
8. Slugg PH, *et al.* Ranitidine pharmacokinetics and adverse central nervous system reactions. *Arch Intern Med* 1992; **152:** 2325–9.
9. Price W, *et al.* Ranitidine-associated hallucinations. *Eur J Clin Pharmacol* 1985; **29:** 375–6.
10. Epstein CM. Ranitidine. *N Engl J Med* 1984; **310:** 1602.
11. Nicholson AN, Stone BM. The H -antagonists, cimetidine and ranitidine: studies on performance. *Eur J Clin Pharmacol* 1984; **26:** 579–82.

Effects on the skin. A report of vasculitic rash occurring in 3 patients undergoing ranitidine therapy.[1] In each case the rash cleared after withdrawal of the drug.

See also under Hypersensitivity, below, and also Cimetidine, p.1717.

1. Haboubi N, Asquith P. Rash mediated by immune complexes associated with ranitidine treatment. *BMJ* 1988; **296:** 897.

Fever. A report[1] of pyrexia associated with ranitidine. Apart from raised temperature the patient was otherwise well; fever resolved on stopping ranitidine and recurred on rechallenge.

1. Kavanagh GM, *et al.* Ranitidine fever. *Lancet* 1993; **341:** 1422.

Hypersensitivity. Respiratory stridor and an urticarial rash occurred in a patient shortly after taking the first dose of ranitidine;[1] the symptoms responded to adrenaline subcutaneously.

1. Brayko CM. Ranitidine. *N Engl J Med* 1984; **310:** 1601–2.

Meningitis. A 30-year-old man developed aseptic meningitis on 3 occasions after use of ranitidine.[1] In each case symptoms resolved rapidly on withdrawal of the drug.

1. Durand JM, *et al.* Ranitidine and aseptic meningitis. *BMJ* 1996; **312:** 886. Correction. *ibid.*; 1392.

Precautions

As for Cimetidine, p.1718.

Helicobacter pylori testing. For reference to the effect of ranitidine on the urea breath test for *Helicobacter pylori*, see p.1718.

Hepatic impairment. Sixteen of 27 patients with cirrhosis of the liver and indications for treatment with an H_2-antagonist (peptic ulcer, gastritis, or reflux oesophagitis) failed to respond to ranitidine 300 mg compared with 6 failures from 32 patients without cirrhosis. Famotidine 40 mg was given to 10 of the cirrhotic nonresponders and 8 still had no response; 7 of these patients were given cimetidine 800 mg and only 1 responded. In the control group, all 3 patients given famotidine did not respond and only 1 responded when given cimetidine. It was concluded that the incidence of non-response to H_2-antagonists is increased in patients with liver cirrhosis but no explanation could be given for this effect.[1] Interestingly there is an earlier report of patients with cirrhosis demonstrating increased bioavailability and decreased clearance of ranitidine.[2]

1. Walker S, *et al.* Frequent non-response to histamine H -receptor antagonists in cirrhotics. *Gut* 1989; **30:** 1105–9.
2. Young CJ, *et al.* Effects of cirrhosis and ageing on the elimination and bioavailability of ranitidine. *Gut* 1982; **23:** 819–23.

Porphyria. Ranitidine is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Renal impairment. For evidence of reduced clearance of ranitidine in patients with renal impairment see Administration in Renal Impairment, below.

Interactions

Unlike cimetidine (p.1718), ranitidine does not seem to affect cytochrome P450 to any great extent, and therefore is considered to have little effect on the metabolism of other drugs. However, as with other H_2-antagonists, its effects on gastric pH may alter the absorption of some other drugs.

◊ A review comparing the drug interactions of ranitidine with those of cimetidine.[1]

1. Smith SR, Kendall MJ. Ranitidine versus cimetidine: a comparison of their potential to cause clinically important drug interactions. *Clin Pharmacokinet* 1988; **15:** 44–56.

Cisapride. Peak plasma concentrations of ranitidine were achieved more rapidly in 12 healthy subjects who also took cisapride.[1] The clinical significance is questionable and such combinations have been used clinically, although the use of cisapride is now restricted in most countries.

1. Rowbotham DJ, *et al.* Effect of single doses of cisapride and ranitidine administered simultaneously on plasma concentrations of cisapride and ranitidine. *Br J Anaesth* 1991; **67:** 302–305.

Pharmacokinetics

Ranitidine is readily absorbed from the gastrointestinal tract with peak concentrations in plasma occurring about 2 to 3 hours after oral doses. Food does not significantly impair absorption. The bioavailability of ranitidine after oral doses is about 50%. Ranitidine is rapidly absorbed on intramuscular injection, with peak plasma concentrations occurring in about 15 minutes. It is weakly bound, about 15%, to plasma proteins.

The elimination half-life is about 2 to 3 hours and is increased in renal impairment. A small proportion of ranitidine is metabolised in the liver to the *N*-oxide, the *S*-oxide, and desmethylranitidine; the *N*-oxide is the major metabolite but accounts for only about 4 to 6% of a dose. About 30% of an oral dose and 70% of an intravenous dose is excreted unchanged in the urine in

24 hours, primarily by active tubular secretion; there is some excretion in the faeces. Ranitidine crosses the placental barrier and is distributed into breast milk.

Distribution into breast milk. A study in a mother given multiple doses of ranitidine showed higher concentrations in breast milk than in serum; the minimum milk concentration occurred between 1 and 2 hours after a dose and the highest concentration was towards the end of the 12-hour dosing interval.[1] The amount that would be ingested by the infant could not be reliably estimated because of the variable milk to serum ratio.

1. Kearns GL, *et al.* Appearance of ranitidine in breast milk following multiple dosing. *Clin Pharm* 1985; **4:** 322–4.

Enterohepatic recycling. Some individuals have a second peak in the plasma concentration of ranitidine, which could be due to enterohepatic recirculation. However, only 0.7 to 2.6% and 0.3 to 1.0% of a dose of ranitidine was excreted into the bile of 3 patients in 24 hours after 50 mg given intravenously or 300 mg by mouth respectively, indicating that significant recirculation did not occur.[1]

1. Klotz U, Walker S. Biliary excretion of H -receptor antagonists. *Eur J Clin Pharmacol* 1990; **39:** 91–2.

Neonates. Renal function is limited in the first month of life, and reduced clearance of ranitidine would be expected. Blood samples taken from 27 full-term neonates given a single intravenous dose of ranitidine 2.4 mg/kg revealed the following pharmacokinetic data: elimination half-life, 3.45 hours; total volume of distribution, 1.52 litres/kg; total plasma clearance, 5.02 mL/kg per minute.[1] None of the infants had renal or hepatic impairment. In another study,[2] an elimination half-life of 6.61 hours was found in 13 full-term neonates given ranitidine 2 mg/kg. See also Administration in Children, below.

1. Fontana M, *et al.* Ranitidine pharmacokinetics in newborn infants. *Arch Dis Child* 1993; **68:** 602–3.
2. Wells TG, *et al.* Pharmacokinetics and pharmacodynamics of ranitidine in neonates treated with extracorporeal membrane oxygenation. *J Clin Pharmacol* 1998; **38:** 402–7.

Uses and Administration

Ranitidine is a histamine H_2-antagonist with actions and uses similar to those of cimetidine (p.1719).

Ranitidine may be given orally or parenterally by the intravenous or intramuscular routes. Although most preparations contain ranitidine hydrochloride, strengths and doses are expressed in terms of the base. Ranitidine hydrochloride 111.6 mg is equivalent to about 100 mg of ranitidine.

In the management of benign **gastric** and **duodenal ulceration** (p.1702) a single daily oral dose of 300 mg at bedtime or 150 mg twice daily (in the morning and at bedtime) is given initially for at least 4 weeks. A dose of 300 mg twice daily may also be used in duodenal ulcer. Where appropriate a maintenance dose of 150 mg daily may be given at bedtime. Ranitidine 150 mg twice daily may be given during therapy with NSAIDs for prophylaxis against duodenal ulceration. A suggested dose for the treatment of peptic ulcer in children is 2 to 4 mg/kg twice daily to a maximum of 300 mg in 24 hours; a maintenance dose of 2 to 4 mg/kg once daily may be used, to a maximum of 150 mg daily.

For duodenal ulcer associated with *Helicobacter pylori* infection, ranitidine in a usual oral dose of 300 mg once daily or 150 mg twice daily may be given as part of triple therapy with amoxicillin 750 mg and metronidazole 500 mg, both three times daily, for 2 weeks. Therapy with ranitidine should then be continued for a further 2 weeks.

In **gastro-oesophageal reflux disease** (p.1696) the oral dose is 150 mg twice daily or 300 mg at bedtime for up to 8 weeks or, if required, 12 weeks. This may be increased to 150 mg four times daily for up to 12 weeks in severe cases. In the maintenance of healing erosive oesophagitis, a dose of 150 mg twice daily may be used. Although there is limited data on the use of ranitidine for gastro-oesophageal reflux disease and erosive oesophagitis in children, a dose of 5 to 10 mg/kg daily, usually given in 2 divided doses, has been used. In pathological hypersecretory conditions, such as the **Zollinger-Ellison syndrome**, (p.1704) the initial oral dose is usually 150 mg twice or three times daily and may be increased if necessary; doses of up to 6 g daily have been used. Alternatively, an intravenous infusion may be given, initially at a rate of 1 mg/kg per hour; the rate may be increased by increments of 500 micrograms/kg per hour, beginning after 4 hours, if required.

For the management of patients at risk from **stress ulceration** of the upper gastrointestinal tract, parenteral therapy may be given as a slow intravenous injection of a 50-mg priming dose followed by a continuous intravenous infusion of 125 to 250 micrograms/kg per hour. Oral doses of 150 mg twice daily may be given once oral feeding is resumed.

In patients at risk of developing the **acid aspiration syndrome** (p.1693) during general anaesthesia, an oral dose of 150 mg may be given 2 hours before the induction of anaesthesia and preferably also 150 mg the previous evening. Alternatively, a dose of 50 mg may be given by intramuscular or slow intravenous injection 45 to 60 minutes before the induction of anaesthesia. In obstetric patients, at the start of labour an oral dose of 150 mg may be given and may be repeated at intervals of 6 hours if required.

In patients with chronic episodic **dyspepsia** (p.1695), a dose of 150 mg twice daily orally for up to 6 weeks may be given. For the short-term symptomatic relief of dyspepsia a dose of 75 mg, repeated if necessary up to a maximum of 4 doses daily, may be taken. Treatment should be restricted to a maximum of 2 weeks of continuous use at one time.

PARENTERAL DOSAGE.

The usual dose of ranitidine by intramuscular or intravenous injection is 50 mg, which may be repeated every 6 to 8 hours; the intravenous injection should be given slowly over not less than 2 minutes and should be diluted to contain 50 mg in 20 mL. For an intermittent intravenous infusion the recommended dose in the UK is 25 mg/hour given for 2 hours which may be repeated every 6 to 8 hours. A rate of 6.25 mg/hour has been suggested for continuous intravenous infusion although higher rates may be used for conditions such as Zollinger-Ellison syndrome or in patients at risk from stress ulceration (see above).

DOSAGE IN RENAL IMPAIRMENT.

For dosage in renal impairment, see below.

Administration in children. The disposition of ranitidine in children is not significantly different from that in young adults and an oral dose of 2 mg/kg (about equal to an adult dose of 150 mg) has been used for the prevention of acid aspiration in children undergoing surgery.[1] A study in premature infants being treated with dexamethasone for bronchopulmonary dysplasia found that infusion of ranitidine 62.5 micrograms/kg per hour was sufficient to raise and maintain gastric pH above 4 to help protect against gastrointestinal bleeding and perforation.[2] Another study found 500 micrograms/kg twice daily to be sufficient for preterm infants, but that 1.5 mg/kg three times daily was needed for full-term infants.[3] A minimum dosage of 3 mg/kg daily was suggested for stress ulcer prophylaxis in older infants and children.[4]

1. Christensen S, *et al.* Effects of ranitidine and metoclopramide on gastric fluid pH and volume in children. *Br J Anaesth* 1990; **65:** 456–60.
2. Kelly EJ, *et al.* The effect of intravenous ranitidine on the intragastric pH of preterm infants receiving dexamethasone. *Arch Dis Child* 1993; **69:** 37–9.
3. Kuusela A-L. Long term gastric pH monitoring for determining optimal dose of ranitidine for critically ill preterm and term neonates. *Arch Dis Child Fetal Neonatal Ed* 1998; **78:** F151–F153.
4. Harrison AM, *et al.* Gastric pH control in critically ill children receiving intravenous ranitidine. *Crit Care Med* 1998; **26:** 1433–6.

Administration in renal impairment. A study in patients with varying degrees of renal impairment[1] found that the mean terminal half-life of ranitidine was increased from 2.09 hours in subjects with normal renal function to between 4.23 and 8.45 hours in patients with renal impairment, the degree of prolongation being proportional to the degree of impairment as measured by glomerular filtration rate. As a result of these findings it was recommended that the dose of ranitidine should be halved in patients with a glomerular filtration rate of 20 mL/minute or less. Licensed drug information therefore recommends that dosage of ranitidine be reduced in patients with severe renal impairment.

For patients with a creatinine clearance of less than 50 mL/minute, an *oral* dose of 150 mg daily is recommended, which may be cautiously increased to 150 mg every 12 hours if needed.

For *intravenous* use, licensed recommendations vary between countries. In the UK, individual doses may be reduced to 25 mg, while the frequency is adjusted in the USA to give a recommended usual dose of 50 mg every 18 to 24 hours, which may be cautiously increased to every 12 hours or more often if necessary.

Ranitidine 150 mg daily provided adequate serum concentrations without excessive accumulation in 20 patients undergoing regular haemodialysis.[2] The serum-ranitidine concentrations fell by about 50% during a 4-hour haemodialysis session but less than 3% of the dose was removed and supplemental doses after dialysis were considered unnecessary.

1. Dixon JS, *et al.* The effect of renal function on the pharmacokinetics of ranitidine. *Eur J Clin Pharmacol* 1994; **46:** 167–71.
2. Comstock TJ, *et al.* Ranitidine accumulation in patients undergoing chronic hemodialysis. *J Clin Pharmacol* 1988; **28:** 1081–5.

Cystic fibrosis. A comparative study involving 29 patients with cystic fibrosis (p.166) found that ranitidine was more effective than cisapride in improving dyspeptic symptoms and gastric emptying and distension.[1] Antisecretory drugs are also used in this condition to decrease the inactivation of oral pancreatic enzyme therapy.

1. Cucchiara S, *et al.* Ultrasound measurement of gastric emptying time in patients with cystic fibrosis and effect of ranitidine on delayed gastric emptying. *J Pediatr* 1996; **128:** 485–8.

Immunomodulation. Like cimetidine (see p.1719), ranitidine has been proposed to have immunoregulatory effects. However, ranitidine 300 mg twice daily had no effect on absolute CD4 cell counts or plasma HIV RNA in patients with HIV infection in a placebo-controlled study.[1] Similarly, ranitidine had no significant benefit in patients with gastric cancer (see Malignant Neoplasms, p.1719).

1. Bartlett JA, *et al.* A placebo-controlled trial of ranitidine in patients with early human immunodeficiency virus infection. *J Infect Dis* 1998; **177:** 231–4.

Skin disorders. As with cimetidine (p.1720), ranitidine has been tried in various skin disorders. Ranitidine 300 mg twice daily by mouth has been reported to be of benefit as an adjuvant to local treatment with corticosteroids and a moisturising ointment in patients with *atopic dermatitis*.[1] There are reports of improvements in *psoriasis* after use of ranitidine,[2-4] although this is a field that is notoriously difficult to evaluate because of the chronic relapsing and remitting nature of the disease, and others have failed to show benefit.[5]

1. Veien NK, *et al.* Ranitidine treatment of hand eczema in patients with atopic dermatitis: a double-blind placebo-controlled trial. *J Am Acad Dermatol* 1995; **32:** 1056–7.
2. Witkamp L, *et al.* An open prospective clinical trial with systemic ranitidine in the treatment of psoriasis. *J Am Acad Dermatol* 1993; **28:** 778–81.
3. Smith KC. Ranitidine useful in the management of psoriasis in a patient with acquired immunodeficiency syndrome. *Int J Dermatol* 1994; **33:** 220–1.
4. Kristensen JK, *et al.* Systemic high-dose ranitidine in the treatment of psoriasis: an open prospective clinical trial. *Br J Dermatol* 1995; **133:** 905–8.
5. Çetin L, *et al.* High-dose ranitidine is ineffective in the treatment of psoriasis. *Br J Dermatol* 1997; **137:** 1021–2.

Preparations

BP 2008: Ranitidine Injection; Ranitidine Oral Solution; Ranitidine Tablets; ***USP 31:*** Ranitidine in Sodium Chloride Injection; Ranitidine Injection; Ranitidine Oral Solution; Ranitidine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Acidex; Alivian; Aludrox AC†; Aprical†; Ciscomax†; Dualid; Espaven; Faboacid-R; Fendibina; Gastrial; Gastrolets; Gastrosedol; Gastrozac; Insuflen†; Lorbitidina; Luvier; Notrab; Prednocris; Ranimed; Ranitic; Ranitidi GNO†; Ranitral; Ranitul; Raticina; Reco; Reflux; Sustac; Taural; Telus†; Teogrand; Tomag†; Ulcotenk; Urgis; Vingional; Vizerul; Zantac; ***Austral.:*** Ausran; Heartburn Relief†; Rani 2; Ranihexal; Ranitic; Ranoxyl; Ulcaid; Zantac; ***Austria:*** Ranic; Raninorm; Ranityrol†; Ulsal; Zantac; Zantarac; ***Belg.:*** Docraniti; Gastran; Zantac; ***Braz.:*** Antagon; Antak; Antidin; Aziliv; Gastrat†; Label; Logat; Neosac; Nititom†; Prevulcer†; Rabiodina†; Radan†; Raniclor; Ranidin; Ranidina; Ranidine; Raniflex†; Ranitak†; Ranitil; Ranitin; Ranitinol; Ranition; Ranitrat; Ranitzen†; Ranizol†; Ranytisan†; Rhanitak†; Tazepin†; Ulceridina; Ulcerit†; Ulcerocin; Ulcoren; Ultidin; Zadine†; Zylium; ***Canad.:*** Acid Reducer; Novo-Ranidine; Nu-Ranit; Zantac; ***Chile:*** Aciflux†; Ranicel; Ranitax; Tipac; Zantac; ***Cz.:*** Arnetin†; Histac; Raniberl†; Ranisan; Ranital; Ranitin†; Ulcosan; Ulran†; Zantac; ***Denm.:*** Aducin†; Kuracid; Ranicodan; Ranikur†; Zantac; ***Fin.:*** Esofex†; Inside Brus; Ranicur; Ranil; Ranimex; Ranixal; Zantac; ***Fr.:*** Azantac; Raniplex; ***Ger.:*** Azuranit†; Junizac; Phamoranit†; Ran Lich; Rani; Rani-nerton; Raniberl; Ranibeta; Ranibloc; Ranicux; Ranidura T; Ranimerck; Raniprotect; Ranitab; Ranitic; Ranitidoc; Sostril; Zantic; ***Gr.:*** Alphadine; Aova; B-Alcerin†; Baroxal; Bindazac; Blumol; Brixoral; Ceftrinal; Epadoren; Ezopta; Galebiron; Gaproxen; Gertocalm; Lomadryl; Lumaren; Narigen; Nipodur; Nitised; Odanet†; Ptinolin; Raniclon; Ranizac; Restopon; Ribolin; Rothonal; Semuele; Smaril; Soredine†; Specinor; Sveltanet; Synthomanet; Tupast; Verlost; Yara; Zantac; Zoliden; Zurfix; ***Hong Kong:*** Gastril†; Hyzan; LAtac; Lumeran; Novo-Ranidine; Radin; Ranolta; Simetac; Synitidine; Ulticer; Zantac; Zendhin; ***Hung.:*** Histac; Huma-Ranidine†; Ranitic; Ulceran; Ulcosin; Umaren; Xanomel†; Zantac; ***India:*** Aciloc; Consec; Histac; R-Loc; Rantac†; Ultac; Zinetac; ***Indon.:*** Acran; Aldin; Anitid; Chopintac; Conranin; Fordin; Gastridin; Hexer; Radin; Rancus; Ranilex; Ranin; Ranticid; Rantin; Ratinal; Renatac; Scanarin; Tricker; Ulceranin; Wiacid; Xeradin; Zantac; Zantadin; Zumaran; ***Irl.:*** Gertac; Ranitic; Ranopine; Xanomel; Zandine†; Zantac; ***Israel:*** Zanidex; Zantac; ***Ital.:*** Dolilux; Duoran†; Raniben; Ranibloc; Ranidex; Ranidil; Sensigard; Ulcex; Zantac; ***Jpn:*** Zantac; ***Malaysia:*** Arnetin; Histac; Hyzan†; Rintac†; Vesyca; X'tac; Zantac; Zendhin; ***Mex.:*** Acloral; Agrisen; Aldivina; Alter-H †; Alvidina†; Anistal; Anticina; Apoprin†; Avintac; Azantac; Cauteridol; Credaxol; Dinaxin; Driges; Flatmed; Galidrin; Gastrec; Gastridin; Gasyran†; Iqfadina; Katalem; Microdit†; Microtid; Midaven; Neugal; Offentina; Radyn; Ranepal; Ranifarm; Ranifur; Raniger; Ranisen; Ranulin†; Ranzil†; Raudil; Redacid; Serranit; Serviradine; Sinhcloran; Syngasy; Terodul; Tianak; Ulcedin†; Ulcevit; Ulgastrin; Ulkodin; Ulmodhyl; Ulsaven; Ultran; Unitin; ***Neth.:*** Azantac; Zantac; ***Norw.:*** Inside Brus; Zantac; ***NZ:*** Zantac; ***Philipp.:*** Aceptin; Aciloc; Ameket; Ceranid; Dalycrid; Danitin; Eu-Ran; Incid; Mordek; Pep-Bloc; Ramadine; Ranitab; Rapidin; Raxide; Renfort; Ulcemed; Ulceragon; Ulceral; Ulcergo; Ulcerix; Ulcin; Ulran; Zantac; Zeptag; ***Pol.:*** Gastranin Zdrovit; Novo-Ranidine; Raniberl; Ranic; Ranigast; Ranimax; Ranisan; Ranitin; Riflux; Solvertyl; Zantac; ***Port.:*** Bloculcer; Gastridina; Gas-

trolav; Gastrulcer; Pep-Rani; Peptab; Peptifar; Quardin†; Ran†; Ranitine; Stacer; Ulcecur†; Ulcerol†; Zantac; ***Rus.:*** Aciloc (Ацилок); Histac (Гистак); Ranigast (Ранигаст); Ranisan (Ранисан); Rantac (Рантак); Ulran (Ульран)†; Zantac (Зантак); Zoran (Зоран); ***S.Afr.:*** GI-Tak†; Histak; Ranihexal; Ranteen†; Ulcaid; Ultak; Zantac; ***Singapore:*** Gastran†; Histac; Hyzan; Lumaren; Neoceptin-R; Rani†; Ranidine; Ratic; Xanidine; Zantac; Zendhin; Zoran†; ***Spain:*** Alquen; Arcid; Ardoral; Coralen; Denulcer; Fagus; Lake; Meticel†; Quantor; Ran H2; Ranidin; Ranix; Ranuber; Rubiulcer; Tanidina; Terposen; Toriol; Underacid; Zantac; ***Swed.:*** Artonil; Inside; Rani-Q; Zantac; ***Switz.:*** Ranimed; Ranisifar; Ulcidine; Zantic; ***Thai.:*** Aciloc; Histac; Radine†; Ranicid; Ranidine; Rantac; Ratic; Ratica; Utac; Xanidine; Zanamet; Zantac; Zantidon; Zardil; ***Turk.:*** Ranitab; Ranitine; Ranobel; Rozon; Santanol; Ulcuran; Zandid; Zantac; ***UAE:*** Rantag; ***UK:*** Gavilast; Ranitic; Ranitil; Rantec; Ranzac; Vivatak†; Zaedoc†; Zantac; ***USA:*** Zantac; ***Venez.:*** Aplom; Enteral; Gastac; Ranibloc; Ranifesa†; Ranix†; Ranizan†; Retamin; Vizerul; Zantac; Zoran†.

Multi-ingredient: ***Arg.:*** Duo Vizerul†; Euciton Reflux; Megalex; ***India:*** Aciloc RD; ***Mex.:*** Ergex.

Ranitidine Bismuth Citrate *(BAN, USAN)*

A complex of ranitidine and bismuth citrate; GR-122311X; Ranitidin Bizmut Sitrat; Ranitidin Bizmutreks; Ranitidina y bismuto, citrato de; Ranitidine Bismutrex. *N*-[2-({5-[(Dimethylamino)methyl]furfuryl}thio)-ethyl]-*N′*-methyl-2-nitro-1,1-ethenediamine, compound with bismuth(3+) citrate (1:1).

Ранитидин Висмут Цитрат

$C_{13}H_{22}N_4O_3S,C_6H_5BiO_7$ = 712.5.

CAS — 128345-62-0.

ATC — A02BA07.

ATC Vet — QA02BA07.

Adverse Effects and Precautions

Ranitidine bismuth citrate would be expected to combine the adverse effects of both bismuth compounds (p.1711) and ranitidine (p.1766). Blackening of the tongue and faeces is common, and gastrointestinal disturbances, headache, mild anaemia, and altered liver enzyme values have been reported. Rarely, hypersensitivity reactions (including anaphylaxis), have occurred.

Ranitidine bismuth citrate should not be given to patients with moderate to severe renal impairment. It is not suitable for long-term or maintenance therapy because of the risk of bismuth accumulation. As with other antisecretory drugs, the possibility of malignancy should be considered when giving ranitidine bismuth citrate to patients with gastric ulcers since the drug may mask symptoms and delay diagnosis.

Interactions

Ranitidine bismuth citrate would be expected to have the interactions of bismuth compounds (p.1712), and ranitidine (p.1766).

Pharmacokinetics

After oral doses, ranitidine bismuth citrate dissociates into its ranitidine and bismuth components in the stomach. For the pharmacokinetics of ranitidine, see p.1766, and for those of bismuth, see p.1712.

◊ References.

1. Lacey LF, *et al.* Comparative pharmacokinetics of bismuth from ranitidine bismuth citrate (GR122311X), a novel anti-ulcerant and tripotassium dicitrato bismuthate (TDB). *Eur J Clin Pharmacol* 1994; **47:** 177–80.
2. Koch KM, *et al.* Pharmacokinetics of bismuth and ranitidine following single doses of ranitidine bismuth citrate. *Br J Clin Pharmacol* 1996; **42:** 201–5.
3. Koch KM, *et al.* Pharmacokinetics of bismuth and ranitidine following multiple doses of ranitidine bismuth citrate. *Br J Clin Pharmacol* 1996; **42:** 207–11.

Uses and Administration

Ranitidine bismuth citrate is a complex of ranitidine with bismuth and citrate, which releases ranitidine and bismuth in the gastrointestinal tract and therefore possesses both the actions of the bismuth compounds (p.1712) and of ranitidine (p.1767). It has been used in the management of peptic ulcer disease (p.1702), and may be given with antibacterials for the eradication of *Helicobacter pylori* infection and the prevention of relapse of peptic ulcer disease.

Doses are 400 mg twice daily orally; treatment has usually been given for 4 to 8 weeks for duodenal ulceration and for 8 weeks for benign gastric ulceration. Ranitidine bismuth citrate should not be used for maintenance therapy, and a maximum of 16 weeks of treatment (two 8-week courses or four 4-week courses) may be given in a 12-month period. For duodenal ulceration where *H. pylori* infection is present, ranitidine bismuth citrate has been given as part of a 7-day triple therapy regimen, typically combined with any two of clarithromycin 500 mg twice daily, amoxicillin 1 g twice daily, or metronidazole 400 mg twice daily. Alternatively, a 14-day dual therapy regimen of ranitidine bismuth citrate combined with clarithromycin 500 mg two or three times daily has been used. In both regimens ranitidine bismuth citrate alone may be continued to a total of 28 days.

◊ References.

1. Bardhan KD, *et al.* GR122311X (ranitidine bismuth citrate), a new drug for the treatment of duodenal ulcer. *Aliment Pharmacol Ther* 1995; **9:** 497–506.
2. Peterson WL, *et al.* Ranitidine bismuth citrate plus clarithromycin is effective for healing duodenal ulcers, eradicating H.pylori and reducing ulcer recurrence. *Aliment Pharmacol Ther* 1996; **10:** 251–61.
3. Anonymous. Pylorid, H. pylori and peptic ulcer. *Drug Ther Bull* 1996; **34:** 69–70.
4. van der Wouden EJ, *et al.* One-week triple therapy with ranitidine bismuth citrate, clarithromycin and metronidazole versus two-week dual therapy with ranitidine bismuth citrate and clarithromycin for Helicobacter pylori infection: a randomized, clinical trial. *Am J Gastroenterol* 1998; **93:** 1228–31.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Pylorid†; ***Austria:*** Helirad; Pylorisin; ***Belg.:*** Pylorid†; ***Braz.:*** Pylorid; ***Cz.:*** Eradipak†; ***Denm.:*** Pylorid†; ***Fin.:*** Pylorid; ***Gr.:*** Pylorid; ***Hong Kong:*** Pylorid†; ***Hung.:*** Pylorid†; ***Irl.:*** Pylorid†; ***Ital.:*** Elicodil†; Pylorid; ***Mex.:*** Azanplus; ***Neth.:*** Pylorid†; ***Norw.:*** Pylorid; ***Port.:*** Pylorid†; ***Spain:*** Pylorid; ***Switz.:*** Pylorid†; ***Thai.:*** Pylorid†; ***Turk.:*** Pylorid; ***UK:*** Pylorid†; ***Venez.:*** Pylorid.

Multi-ingredient: ***Austral.:*** Pylorid-KA.

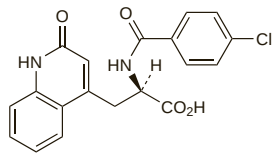
Rebamipide *(rINN)*

Rebamipida; Rébamipide; Rebamipidum. (±)-α-(*p*-Chlorobenzamido)-1,2-dihydro-2-oxo-4-quinolinepropionic acid.

Ребамипид

$C_{19}H_{15}ClN_2O_4$ = 370.8.

CAS — 90098-04-7; 111911-87-6.



and enantiomer

Profile

Rebamipide is stated to possess cytoprotective properties and is used in the treatment of peptic ulcer disease (p.1702) and gastritis in usual oral doses of 100 mg three times daily. It has also been used rectally for the treatment of intestinal inflammation. Rebamipide eye drops are under investigation in the treatment of dry eye.

◊ References.

1. Makiyama K, *et al.* Efficacy of rebamipide enemas in active distal ulcerative colitis and proctitis: a prospective study report. *Dig Dis Sci* 2005; **50:** 2323–9.
2. Miyata M, *et al.* Successful treatment of severe pouchitis with rebamipide refractory to antibiotics and corticosteroids: a case report. *World J Gastroenterol* 2006; **12:** 656–8.
3. Miwa H, *et al.* Effect of a gastro-protective agent, rebamipide, on symptom improvement in patients with functional dyspepsia: a double-blind placebo-controlled study in Japan. *J Gastroenterol Hepatol* 2006; **21:** 1826–31.

Preparations

Proprietary Preparations (details are given in Part 3)

Indon.: Mucosta; ***Jpn:*** Mucosta; ***Philipp.:*** Mucosta; ***Thai.:*** Mucosta.

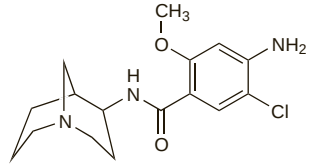
Renzapride *(BAN, rINN)*

ATL-1251; BRL-24924A; Renzaprida; Renzapridum. (±)-*endo*-4-Amino-*N*-(1-azabicyclo[3.3.1]non-4-yl)-5-chloro-*o*-anisamide.

Рензаприд

$C_{16}H_{22}ClN_3O_2$ = 323.8.

CAS — 88721-77-1; 112727-80-7.



Profile

Renzapride is a substituted benzamide with prokinetic actions on gastrointestinal motility. It also has 5-HT_4 agonist and 5-HT_3 antagonist activity. It is under investigation for the management of gastrointestinal disorders including irritable bowel syndrome.

◊ References.

1. Tack J, *et al.* Pilot study of the efficacy of renzapride on gastrointestinal motility and symptoms in patients with constipation-predominant irritable bowel syndrome. *Aliment Pharmacol Ther* 2006; **23:** 1655–65.
2. George AM, *et al.* Clinical trial: renzapride therapy for constipation-predominant irritable bowel syndrome—multicentre, randomized, placebo-controlled, double-blind study in primary healthcare setting. *Aliment Pharmacol Ther* 2008; **27:** 830–7.

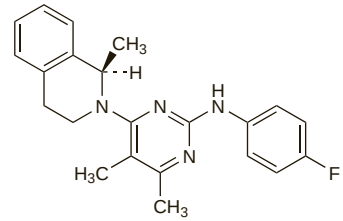
Revaprazan *(rINN)*

Révaprazan; Revaprazán; Revaprazanum. *N*-(4-Fluorophenyl)-4,5-dimethyl-6-[(1*RS*)-1-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]pyrimidin-2-amine.

Реваразан

$C_{22}H_{23}FN_4$ = 362.4.

CAS — 199463-33-7.



Revaprazan Hydrochloride *(USAN, rINNM)*

Hidrocloruro de revaprazán; Révaprazan, Chlorhydrate de; Revaprazani Hydrochloridum; YH-1238; YH-1885. *N*-(4-Fluorophenyl)-5,6-dimethyl-4-[(1*RS*)-1-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl]pyrimidin-2-amine hydrochloride.

Реваразана Гидрохлорид

$C_{22}H_{23}FN_4,HCl$ = 398.9.

CAS — 178307-42-1.

Profile

Revaprazan is a proton pump inhibitor that is under investigation for the management of gastric and duodenal ulceration, functional dyspepsia, and gastro-oesophageal reflux disease.

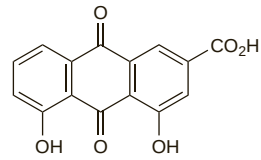
◊ References.

1. Sorbera LA, *et al.* Revaprazan hydrochloride. *Drugs Of The Future* 2004; **29:** 455.
2. Yu K-S, *et al.* Pharmacokinetic and pharmacodynamic evaluation of a novel proton pump inhibitor, YH1885, in healthy volunteers. *J Clin Pharmacol* 2004; **44:** 73–82.

Rhubarb

Chinese Rhubarb; Korzeń rzewienia; Rabarbaro; Rabarbarų šaknys; Rabarberrot; Raparperinjuuri; Ravent; Rebarbara-gyökértörzs; Reveňový kořen; Rhabarber; Rhei radix; Rhei Rhizoma; Rheum; Rhubarb Rhizome; Rhubarbe; Ruibarbo.

Ревень Аптечный



(rhein)

Description. Indian rhubarb (Himalayan rhubarb) consists of the dried rhizome and roots of *Rheum emodi*, *R. webbianum*, or some other related species of *Rheum*.
Rhapontic rhubarb (Chinese rhapontica) consists of the dried rhizomes of *R. rhaponticum*. It may occur as an adulterant of rhubarb, and pharmacopoeias specify a test to confirm its absence. Garden rhubarb, of which the leaf-stalks are used as food, is derived from *R. rhaponticum*.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Jpn. Chin.* and *Jpn* also permit *Rheum tanguticum*, and *Jpn* also permits *R. coreanum*.

Ph. Eur. 6.2 (Rhubarb). The whole or cut, dried underground parts of *Rheum palmatum* or of *R. officinale* or of hybrids of these two species or of a mixture. The underground parts are often divided; the stem and most of the bark with the rootlets are removed. It contains not less than 2.2% of hydroxyanthracene derivatives, expressed as rhein ($C_{15}H_8O_6$ = 284.2), calculated with reference to the dried drug. Protect from light.

Adverse Effects and Precautions

As for Senna, p.1769.

Uses and Administration

Rhubarb is an anthraquinone stimulant laxative used similarly to senna (p.1770). It also exerts an astringent action due to the presence of gallic acid derivatives and tannins.

Homoeopathy. Rhubarb has been used in homoeopathic medicines under the following names: Rheum; Rhei radix; Rheum palmatum.