sorption, may have exacerbated the phosphate-binding effect of the antacid. In another case[5] a dosing error resulted in the infant receiving an excessive dose of antacid for 6 months. The *BNFC* advises against the use of any aluminium-containing antacid in neonates and infants.

Aluminium accumulation resulting in osteomalacia or encephalopathy with seizures and dementia has been reported in children with renal failure (but not on dialysis) treated with aluminium-containing phosphate binders.[6-10] In an adult male patient with severe chronic renal failure who was not on dialysis, self-medication with antacids for at least 3 years resulted in aluminium toxicity associated with encephalopathy, bone disease, and microcytic anaemia.[11] Aluminium-containing antacids should therefore be used with caution in patients with chronic renal failure, especially in children.

Oral citrate salts increase the absorption of aluminium from the gastrointestinal tract[12] and patients with renal failure taking aluminium compounds should avoid citrate-containing preparations, which include many effervescent or dispersible tablets.[13,14] Ascorbic acid has also been reported to enhance aluminium absorption.[15]


1. Flaten TP, *et al*. Mortality from dementia among gastroduodenal ulcer patients. *J Epidemiol Community Health* 1991; **45:** 203–6.
2. Tsou VM, *et al*. Elevated plasma aluminum levels in normal infants receiving antacids containing aluminum. *Pediatrics* 1991; **87:** 148–51.
3. Pivnick EK, *et al.* Rickets secondary to phosphate depletion: a sequela of antacid use in infancy. *Clin Pediatr (Phila)* 1995; **34:** 73–8.
4. Shetty AK, *et al*. Rickets and secondary craniosynostosis associated with long-term antacid use in an infant. *Arch Pediatr Adolesc Med* 1998; **152:** 1243–5.
5. Robinson RF, *et al*. Metabolic bone disease after chronic antacid administration in an infant. *Ann Pharmacother* 2004 **38:** 265–8.
6. Pedersen S, Nathan E. Water treatment and dialysis dementia. *Lancet* 1982; **ii:** 1107.
7. Griswold WR, *et al.* Accumulation of aluminum in a nondialyzed uremic child receiving aluminum hydroxide. *Pediatrics* 1983; **71:** 56–8.
8. Randall ME. Aluminium toxicity in an infant not on dialysis. *Lancet* 1983; **i:** 1327–8.
9. Sedman AB, *et al.* Encephalopathy in childhood secondary to aluminum toxicity. *J Pediatr* 1984; **105:** 836–8.
10. Andreoli SP, *et al*. Aluminum intoxication from aluminum-containing phosphate binders in children with azotemia not undergoing dialysis. *N Engl J Med* 1984; **310:** 1079–84.
11. Zatta P, *et al.* A fatal case of aluminium encephalopathy in a patient with severe chronic renal failure not on dialysis. *Nephrol Dial Transplant* 2004; **19:** 2929–31.
12. Walker JA, *et al*. The effect of oral bases on enteral aluminum absorption. *Arch Intern Med* 1990; **150:** 2037–9.
13. Mees EJD, Basçi A. Citric acid in calcium effervescent tablets may favour aluminium intoxication. *Nephron* 1991; **59:** 322.
14. Main J, Ward MK. Potentiation of aluminium absorption by effervescent analgesic tablets in a haemodialysis patient. *BMJ* 1992; **304:** 1686.
15. Domingo JL, *et al.* Effect of ascorbic acid on gastrointestinal aluminium absorption. *Lancet* 1992; **338:** 1467.


## Interactions

As outlined on p.1692, aluminium compounds used as antacids interact with many other drugs, both by alterations in gastric pH and emptying, and by direct adsorption and formation of complexes that are not absorbed. Interactions can be minimised by giving the aluminium compound and any other medication 2 to 3 hours apart. The absorption of aluminium from the gastrointestinal tract may be enhanced if aluminium compounds are taken with citrates or ascorbic acid (see Toxicity, above).

## Pharmacokinetics

Aluminium hydroxide, given orally, slowly reacts with the hydrochloric acid in the stomach to form soluble aluminium chloride, some of which is absorbed. The presence of food or other factors that decrease gastric emptying prolongs the availability of aluminium hydroxide to react and may increase the amount of aluminium chloride formed. About 100 to 500 micrograms of the cation is reported to be absorbed from standard daily doses of an aluminium-containing antacid, leading to about a doubling of usual aluminium concentrations in the plasma of patients with normal renal function.

Absorbed aluminium is eliminated in the urine, and patients with renal failure are therefore at particular risk of accumulation (especially in bone and the CNS), and aluminium toxicity (see above).

The aluminium compounds remaining in the gastrointestinal tract, which account for most of a dose, form insoluble, poorly absorbed aluminium salts in the intestines including hydroxides, carbonates, phosphates and fatty acid derivatives, which are excreted in the faeces.

## Uses and Administration

Aluminium hydroxide is used as an antacid (p.1692). It is given orally in doses of up to about 1 g, between meals and at bedtime. In order to reduce the constipating effects, aluminium hydroxide is often given with a magnesium-containing antacid, such as magnesium oxide or magnesium hydroxide.

Aluminium hydroxide binds phosphate in the gastrointestinal tract to form insoluble complexes and reduces phosphate absorption. It may thus be used to treat hyperphosphataemia in patients with chronic renal failure (although aluminium accumulation may be a problem—see Renal Osteodystrophy, p.1086) or associated secondary hyperparathyroidism (p.1087). With this use the dose must be adjusted to the individual patient's requirement but up to about 10 g daily may be given orally in divided doses with meals.

Aluminium hydroxide is also used as an adjuvant in adsorbed vaccines.

**Polymyositis and dermatomyositis.** Corticosteroids form the basis of the management of polymyositis (p.1510) but the calcinosis that may occur in dermatomyositis does not always respond well. Aluminium hydroxide 1.68 to 2.24 g daily produced clinical improvement with complete clearing of most calcified nodules after 1 year in a patient with calcinosis cutis complicating juvenile dermatomyositis.[1] The calcified masses are made up of hydroxyapatite and amorphous calcium phosphate and reduction in phosphate absorption by aluminium hydroxide probably helped to reverse their formation. Subsequent cases[2,3] have also reported benefit from aluminium hydroxide treatment in the management of calcinosis.


1. Wang W-J, *et al*. Calcinosis cutis in juvenile dermatomyositis: remarkable response to aluminium hydroxide therapy. *Arch Dermatol* 1988; **124:** 1721–2.
2. Nakagawa T, Takaiwa T. Calcinosis cutis in juvenile dermatomyositis responsive to aluminium hydroxide treatment. *J Dermatol* 1993; **20:** 558–60.
3. Wananukul S, *et al*. Calcinosis cutis presenting years before other clinical manifestations of juvenile dermatomyositis: report of two cases. *Australas J Dermatol* 1997; **38:** 202–5.


## Preparations

***BP 2008:*** Aluminium Hydroxide Oral Suspension; Aluminium Hydroxide Tablets; Co-magaldrox Oral Suspension; Co-magaldrox Tablets; Compound Magnesium Trisilicate Tablets;
***USP 31:*** Alumina and Magnesia Oral Suspension; Alumina and Magnesia Tablets; Alumina and Magnesium Carbonate Oral Suspension; Alumina and Magnesium Carbonate Tablets; Alumina and Magnesium Trisilicate Oral Suspension; Alumina and Magnesium Trisilicate Tablets; Alumina, Magnesia, and Calcium Carbonate Oral Suspension; Alumina, Magnesia, and Calcium Carbonate Tablets; Alumina, Magnesia, and Simethicone Oral Suspension; Alumina, Magnesia, and Simethicone Tablets; Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets; Alumina, Magnesium Carbonate, and Magnesium Oxide Tablets; Aluminum Hydroxide Gel; Aspirin, Alumina, and Magnesia Tablets; Aspirin, Alumina, and Magnesium Oxide Tablets; Dried Aluminum Hydroxide Gel; Dried Aluminum Hydroxide Gel Capsules; Dried Aluminum Hydroxide Gel Tablets.

**Proprietary Preparations** (details are given in Part 3)

***Arg.:*** Pepsamar; ***Austral.:*** Alu-Tab; ***Austria:*** Anti-Phosphat; ***Braz.:*** Aludroxil; Aziram; Biodrox†; Ductogel; Fluagel†; Gastromax; Gastrox; Gelpan†; Hidroxialiv†; Kaogel†; Mylanta Plus; Natusgel†; Noacid†; Pepsamar; Peptgel; ***Canad.:*** Alu-Tab†; Aluge!; Amphojel; Basaljel; ***Chile:*** Risthal†; ***Ger.:*** Aludrox; Anti-Phosphat; ***Gr.:*** Alu-Cap; Pepsamar; ***Hong Kong:*** Alu-Tab; ***India:*** Aludrox; Tricaine-MPS; ***Irl.:*** Aludrox; ***Israel:*** Alu-Cap; ***Ital.:*** Polisilon†; ***Malaysia:*** Alu-Tab; ***Mex.:*** Domigel; Magnalum†; ***NZ:*** Alu-Tab; Amphojel†; ***Philipp.:*** Alu-Tab; ***Pol.:*** Alusal; ***Port.:*** Gelumina†; Pepsamar; ***S.Afr.:*** Alukon; Amphojel; ***Singapore:*** Alu-Tab; ***Spain:*** Aluge!; Pepsamar; ***Switz.:*** Anti-phosphate; Gastracol; ***UK:*** Alu-Cap; Aludrox†; ***USA:*** ALternaGEL; Alu-Cap†; Alu-Tab; Amphojel; Dialume; Nephrox; ***Venez.:*** Gelidral†.

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

*Used as an adjunct in:* ***Arg.:*** Dristan Analgesico†; Dristan Compuesto; Truxa R†; ***Braz.:*** Analtrix†; Butazolon†; Posdrink; Redentil†; Resprax; ***Canad.:*** C2 with Codeine†; ***Chile:*** Silartrin†; ***Fr.:*** Finidol†; ***Gr.:*** Ascriptin†; ***Indon.:*** Naspro; ***Israel:*** Ascriptin†; ***Ital.:*** Ascriptin; Via Mal; ***Mex.:*** Ascriptin; Meprosona-F; ***Switz.:*** Alcacyl; Contre-Douleurs plus; Contre-Douleurs†; ***USA:*** Arthritis Pain Formula; Ascriptin; Asprimox; Cama Arthritis Pain Reliever; Cope; Magnaprin†; Vanquish; ***Venez.:*** Ascriptin.

## Aluminium Hydroxide-Magnesium Carbonate Co-dried Gel

F-MA 11; Hidróxido de aluminio y carbonato de magnesio desecado, gel de.

### Profile

Aluminium hydroxide-magnesium carbonate co-dried gel is a co-precipitate of aluminium hydroxide and magnesium carbonate dried to contain a proportion of water for antacid activity. It is an antacid with general properties similar to those of aluminium hydroxide (above) and magnesium carbonate (p.1743). It has been given in oral doses of about 450 to 900 mg, usually 3 times daily after meals and before bedtime.

### Preparations

**Proprietary Preparations** (details are given in Part 3)

***Denm.:*** Link; ***Fin.:*** Link; РееНоо†; ***Gr.:*** Regla pH†; ***Indon.:*** Stomacain; Veragel; ***Mex.:*** Gelasim; ***Neth.:*** Regla pH; Remegel; ***Norw.:*** Link; ***Swed.:*** Link; ***UK:*** Dijex†.

**Multi-ingredient:** ***Belg.:*** Barexal; Nozid†; Regla pH Forte†; Syngel; ***Braz.:*** Andursil; ***Canad.:*** Diovol; Diovol Plus; Gastrocalm; Thunas Hyperacidity Tablets†; ***Chile:*** Algicote; Disfrutab; Ditopax; ***Fr.:*** Gastropulgite; ***Ger.:*** Colina Spezial; Duoventrinetten N; ***Hong Kong:*** Diovol Plus; Simeco†; Veragel; ***Indon.:*** Aludonna; Di-Gel; Farmacrol; Gastran; Oskamag; Polycrol; Simeco; ***Irl.:*** Algicon†; ***Israel:*** Silain; ***Mex.:*** Algicon†; Ditopax; Ditopax-F; ***Neth.:*** Algicon; Muthesa N; Rigoletten; ***Port.:*** Di-Gel; Di-Gel Forte†; ***Rus.:*** Gastal (Гастал); ***Singapore:*** Meclosil; Veragel DMS; ***Spain:*** Acilene†; Acylene†; ***Switz.:*** Anacidol†; Andursil; Gastropulgite†; Refluxine†; ***Thai.:*** Defomil; Diovol; Kremil; Kremil-S; Machto; Simeco; Veragel; ***UK:*** Algicon†; Simeco; ***Venez.:*** Ditosil.

*Used as an adjunct in:* ***Indon.:*** Rheumapill.

## Aluminium Phosphate

Aliuminio fosfatas; Alumiinifosfaatti; Aluminii phosphas; Aluminio, fosfato de; Aluminium, phosphate d'; Aluminiumfosfat; Alumínium-foszfát; Aluminum Phosphate; Fosfato de aluminio; Fosforečnan hlinitý; Glinu fosforan; Glinu fosforanu.

Алюминия Фосфат

*CAS — 7784-30-7 ($AlPO_4$).*

*ATC — A02AB03.*

*ATC Vet — QA02AB03.*

**Pharmacopoeias.** In *Viet.*

*Eur.* (see p.vii) includes hydrated aluminium phosphate and also a gel. *US* includes as a gel.

**Ph. Eur. 6.2** (Aluminium Phosphate, Hydrated; Aluminii Phosphas Hydricus; Dried Aluminium Phosphate BP 2008). A white or almost white powder. Very slightly soluble in water; practically insoluble in alcohol. It dissolves in dilute solutions of alkali hydroxides and mineral acids. A 4% suspension in water has a pH of 5.5 to 7.2. Store in airtight containers.

**Ph. Eur. 6.2** (Aluminium Phosphate Gel; Aluminii Phosphatis Liquamen). It is aluminium phosphate in gel form containing 19 to 21% of $AlPO_4$. Practically insoluble in water, in alcohol, and in dichloromethane. It dissolves in dilute solutions of mineral acids. pH 6.0 to 8.0. Store in airtight containers.

**USP 31** (Aluminum Phosphate Gel). A 4 to 5% suspension of aluminium phosphate ($AlPO_4$) in water and has a pH of 6.0 to 7.2. It is a white viscous suspension from which small amounts of water separate on standing. Store in airtight containers.

### Profile

Aluminium phosphate is an antacid with general properties similar to those of aluminium hydroxide (p.1706), but it does not produce phosphate depletion.

Aluminium phosphate is also used as an adjuvant in adsorbed vaccines.

### Preparations

***USP 31:*** Aluminum Phosphate Gel.

**Proprietary Preparations** (details are given in Part 3)

***Austria:*** Phosphalugel; ***Belg.:*** Phosphalugel†; ***Cz.:*** Gasterin†; ***Fr.:*** Phosphalugel; ***Ger.:*** Phosphalugel; ***Ital.:*** Fosfalugel; ***Port.:*** Phosphalugel; ***Rus.:*** Phosphalugel (Фосфалюгель); ***Switz.:*** Phosphalugel†.

**Multi-ingredient:** ***Austria:*** Phoscortil; ***Fr.:*** Moxydar; Seroxydar.

## Aluminium Sodium Silicate

E554; Natrii aluminii silicas; Silicato de sodio y de aluminio; Sodium Aluminium Silicate; Sodium Aluminosilicate; Sodium et aluminium, silicate de; Sodium Silicoaluminate.

Алюмосиликат Натрия

*CAS — 1344-00-9.*

### Profile

Aluminium sodium silicate is an antacid with general properties similar to those of aluminium hydroxide (p.1706). Aluminium silicate has been used similarly. They are also used as food additives.

### Preparations

**Proprietary Preparations** (details are given in Part 3)

***Fr.:*** Sulfuryl; ***Port.:*** Acnoil Free.

**Multi-ingredient:** ***Austria:*** Diphlogen; ***Fr.:*** Anti-H†; Cerat Inalterable; Sulfuryl; ***Ger.:*** Enelbin-Paste N; Sulfredox†; ***Hong Kong:*** Epilon; ***Port.:*** Mucal†; ***Thai.:*** Ulgastrin.

## Alverine Citrate *(BANM, USAN, rINNM)*

Alvérine, citrate d'; Alverini citras; Citrato de alverina; Dipropyline Citrate; Phenpropamine Citrate. *N*-Ethyl-3,3′-diphenyldipropylamine citrate.

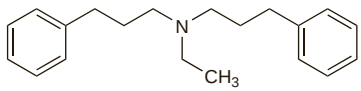
Альверина Цитрат

$C_{20}H_{27}N,C_6H_8O_7$ = 473.6.

*CAS — 150-59-4 (alverine); 5560-59-8 (alverine citrate).*

*ATC — A03AX08.*

*ATC Vet — QA03AX08.*



*(alverine)*

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

**Ph. Eur. 6.2** (Alverine Citrate). A white or almost white crystalline powder. Slightly soluble in water and in dichloromethane; sparingly soluble in alcohol. A 0.5% solution in water has a pH of 3.5 to 4.5. Protect from light.

### Adverse Effects and Precautions

Nausea, headache, pruritus, rash, and dizziness have been reported. Allergic reactions, including anaphylaxis, have also occurred. Alverine is contra-indicated in patients with intestinal obstruction or paralytic ileus.

**Effects on the liver.** Acute hepatitis was attributed to alverine citrate in 2 separate cases.[1,2] Evidence of an immune reaction, including antinuclear antibodies, was found in 1 case.[1]

1. Malka D, *et al.* Acute hepatitis caused by alverine associated with anti-lamin A and C autoantibodies. *J Hepatol* 1997; **27:** 399–403.
2. Arhan M, *et al.* Alverine citrate induced acute hepatitis. *World J Gastroenterol* 2004; **10:** 2303–4.

### Pharmacokinetics

Alverine is absorbed from the gastrointestinal tract after oral doses and is rapidly metabolised to an active metabolite, peak plasma concentrations of which occur 1 to 1.5 hours after an oral dose. Further metabolism to inactive metabolites occurs; metabolites are excreted in the urine by active renal secretion.

### Uses and Administration

Alverine is an antispasmodic that acts directly on intestinal and uterine smooth muscle. It is used for the relief of smooth muscle spasm in the treatment of gastrointestinal disorders such as irritable bowel syndrome (p.1699). It is also used in the treatment of dysmenorrhoea (p.6).

Alverine citrate is given to adults and adolescents from the age of 12 years in oral doses of 60 to 120 mg one to three times daily. Alverine has also been given by suppository as the base. Alverine citrate 67.3 mg is equivalent to about 40 mg of alverine.

**Irritable bowel syndrome.** Alverine citrate is widely used as an antispasmodic in the management of irritable bowel syndrome. However, a 12-week study[1] in 107 patients found that alverine citrate was no better than placebo for the relief of symptoms and improvement in general well-being. A marked placebo effect occurred and symptomatic improvement was reported by at least half the placebo group.

1. Mitchell SA, *et al.* Alverine citrate fails to relieve the symptoms of irritable bowel syndrome: results of a double-blind, randomized, placebo-controlled trial. *Aliment Pharmacol Ther* 2002; **16:** 1187–95.

### Preparations

***BP 2008:*** Alverine Capsules.

**Proprietary Preparations** (details are given in Part 3)

***Belg.:*** Spasmine; ***Hong Kong:*** Profenil; Spasmonal; ***Irl.:*** Spasmonal; ***Malaysia:*** Spasmonal†; ***Pol.:*** Spasmolina; ***Singapore:*** Spasmonal; ***Thai.:*** Spasmonal; ***UK:*** Relaxyl†; Spasmonal.

**Multi-ingredient:** ***Arg.:*** Meteospasmyl; ***Austral.:*** Alvercol†; ***Belg.:*** Normacol Antispasmodique†; ***Cz.:*** Meteospasmyl; ***Fr.:*** Hepatoum; Meteospasmyl; Schoum; ***Hung.:*** Meteospasmyl; ***Indon.:*** Spasmium; ***Malaysia:*** Meteospasmyl; ***Mex.:*** Meteospasmyl; ***Pol.:*** Meteospasmyl; ***Rus.:*** Meteospasmyl (Метеоспазмил); ***S.Afr.:*** Alvercol†; ***Singapore:*** Meteospasmyl; ***Thai.:*** Meteospasmyl; ***Turk.:*** Meteospasmyl; ***UK:*** Spasmonal Fibre†.

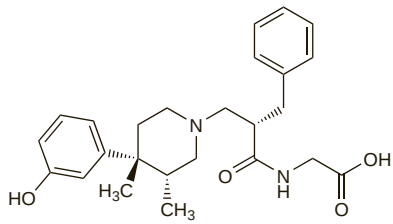
## Alvimopan *(BAN, USAN, rINN)*

ADL-8-2698; Alvimopán; Alvimopanum; LY-246736. [((2*S*)-2-{[(3*R*,4*R*)-4-(3-Hydroxyphenyl)-3,4-dimethylpiperidin-1-yl]methyl}-3-phenylpropanoyl)amino]acetic acid.

Альвимопан

$C_{25}H_{32}N_2O_4$ = 424.5.

*CAS — 156053-89-3 (anhydrous alvimopan); 170098-38-1 (alvimopan dihydrate).*



*(anhydrous alvimopan)*

### Profile

Alvimopan is a peripherally acting selective antagonist of opioid μ-receptors that is used in the treatment of postoperative ileus. It is given in a 12-mg oral dose between 30 minutes and up to 5 hours before surgery followed by 12 mg twice daily beginning the day after surgery for a maximum of 7 days. Alvimopan is also under investigation for opioid-induced constipation.

◊ References.

1. Taguchi A, *et al.* Selective postoperative inhibition of gastrointestinal opioid receptors. *N Engl J Med* 2001; **345:** 935–40.
2. Leslie JB. Alvimopan for the management of postoperative ileus. *Ann Pharmacother* 2005; **39:** 1502–10.
3. Herzog TJ, *et al.* A double-blind, randomized, placebo-controlled phase III study of the safety of alvimopan in patients who undergo simple total abdominal hysterectomy. *Am J Obstet Gynecol* 2006; **195:** 445–53.
4. Tan EK, *et al.* Meta-analysis: Alvimopan vs. placebo in the treatment of post-operative ileus. *Aliment Pharmacol Ther* 2007; **25:** 47–57.

### Preparations

**Proprietary Preparations** (details are given in Part 3)

***USA:*** Entereg.

## Aprepitant *(USAN, rINN)*

Aprépitant; Aprepitantum; L-754030; MK-869; MK-0869. 3-[((2*R*,3*S*)-3-(*p*-Fluorophenyl)-2-{[(α*R*)-α-methyl-3,5-bis(trifluoromethyl)benzyl]oxy}morpholino)methyl]-$\Delta^2$-1,2,4-triazolin-5-one.

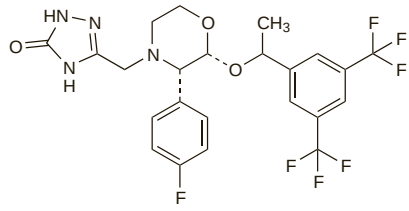
Апрепитант

$C_{23}H_{21}F_7N_4O_3$ = 534.4.

*CAS — 170729-80-3.*

*ATC — A04AD12.*

*ATC Vet — QA04AD12.*



### Adverse Effects and Precautions

The most common adverse effects associated with aprepitant are headache, constipation, diarrhoea, dyspepsia, anorexia, fatigue, hiccups, eructation, and dizziness. Increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) concentrations are common. Other reported effects have included abdominal pain, oedema, tinnitus, and flushing. Epigastric discomfort, dysgeusia, dry mouth, and stomatitis have also occurred. Thirst, polyuria, dysuria, haematuria, urinary frequency, arthralgia, myalgia, bradycardia, hyperglycaemia, disorientation, euphoria, anxiety, photosensitivity, and skin disorders have been reported. Anaemia and febrile neutropenia may occur. Other adverse effects reported include hypertension or hypotension, hyponatraemia, hypokalaemia, insomnia, miosis, reduced visual acuity, weight changes, sensory disturbances, throat irritation, sneezing, abnormal bowel sounds, acid reflux, perforating duodenal ulcer, dyspnoea, cough, wheezing, and hyperhidrosis. Conjunctivitis, pharyngitis, respiratory-tract infections, urinary-tract infections, candidiasis, and herpes simplex can occur. Stevens-Johnson syndrome and angioedema with urticaria have been reported.

Licensed product information recommends caution in patients with severe hepatic impairment as clinical data are lacking in this patient group.

### Interactions

During its use for 3 or 4 days in the prevention of nausea and vomiting associated with cancer chemotherapy, aprepitant produces moderate inhibition of the cytochrome P450 isoenzyme CYP3A4. Exposure to oral CYP3A4 substrates may increase substantially; the effect of aprepitant on intravenous CYP3A4 substrates is expected to be less. However, on cessation of aprepitant a transient mild induction of CYP3A4 may become apparent with a maximum effect reached 3 to 5 days later; this effect is maintained for a few days then slowly declines and is clinically insignificant about 2 weeks after stopping aprepitant. Caution is therefore required when using it with drugs that are primarily metabolised by this isoenzyme. Aprepitant should not be given with astemizole, cisapride, pimozide, or terfenadine as increased plasma concentrations of these drugs could cause serious life-threatening reactions. As aprepitant is also a substrate for CYP3A4, other drugs that inhibit or induce this isoenzyme may in turn increase or decrease plasma concentrations of aprepitant.

When aprepitant is used to prevent postoperative nausea and vomiting, in a single lower dose than that used with cancer chemotherapy, the effect of aprepitant on CYP3A4 is not expected to be clinically significant.

Aprepitant also causes a delayed induction of CYP2C9 and may lower plasma concentrations of drugs metabolised by this isoenzyme, such as warfarin, phenytoin, or tolbutamide.

Aprepitant may increase systemic exposure to corticosteroids; when given together it is recommended that the usual dose of oral dexamethasone be reduced by 50%, and the dose of methylprednisolone by about 25% when given intravenously, and by 50% when given orally. It should be noted that the dose of dexamethasone in the regimens recommended for nausea and vomiting associated with cancer chemotherapy already accounts for this interaction (see Administration, below).

The efficacy of oral contraceptives might be reduced by aprepitant. Licensed product information suggests that alternative methods of contraception should be used during and for 1 to 2 months after stopping any dose of aprepitant.

### Pharmacokinetics

Aprepitant is absorbed from the gastrointestinal tract with peak plasma concentrations achieved after about 4 hours. Bioavailability is about 60% at usual doses. It crosses the blood-brain barrier; plasma protein binding is reported to be more than 95%. Aprepitant undergoes extensive hepatic metabolism, mainly via oxidation by the cytochrome P450 isoenzyme CYP3A4; the isoenzymes CYP1A2 and CYP2C19 mediate minor metabolic pathways. The resultant metabolites have weak activity and are excreted in the urine and in the faeces. Aprepitant is not excreted unchanged in the urine. The terminal half-life is about 9 to 13 hours.

◊ References.

1. Majumdar AK, *et al.* Pharmacokinetics of aprepitant after single and multiple oral doses in healthy volunteers. *J Clin Pharmacol* 2006; **46:** 291–300.

### Uses and Administration

Aprepitant is a neurokinin-1 ($NK_1$) receptor antagonist used in the management of nausea and vomiting (p.1700). It is given orally in doses up to 125 mg, with a corticosteroid and a 5-$HT_3$ antagonist, in the preven-