Alverine Citrate *(BANM, USAN, rINNM)*

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

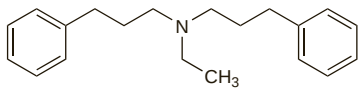
Альверина Цитрат

$C_{20}H_{27}N,C_6H_8O_7$ = 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†.

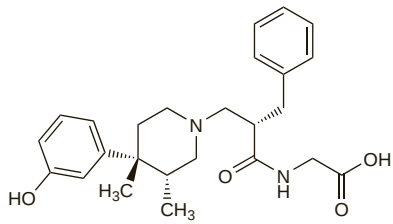
Alvimopan *(BAN, USAN, rINN)*

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]-Δ^2-1,2,4-triazolin-5-one.

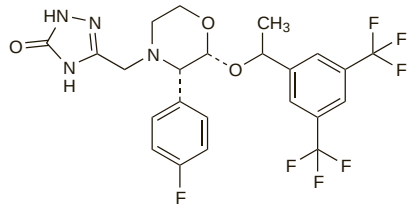
Апрепитант

$C_{23}H_{21}F_7N_4O_3$ = 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-

tion of acute and delayed nausea and vomiting associated with highly emetogenic or moderately emetogenic cancer chemotherapy (for details, see Administration, below).

For the prevention of postoperative nausea and vomiting a single oral dose of aprepitant 40 mg may be given within the 3 hours before induction of anaesthesia.

Administration. Licensed product information for aprepitant suggests the following 4-day regimen for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cancer chemotherapy:

- day 1: aprepitant 125 mg (given 1 hour before chemotherapy) with oral dexamethasone 12 mg and intravenous ondansetron 32 mg (both 30 minutes before chemotherapy)
- days 2 and 3: aprepitant 80 mg with oral dexamethasone 8 mg in the morning
- day 4: oral dexamethasone 8 mg in the morning.

In patients receiving moderately emetogenic chemotherapy, a 3-day regimen has been suggested as follows:

- day 1: aprepitant 125 mg (given 1 hour before chemotherapy) with oral dexamethasone 12 mg (30 minutes before chemotherapy); ondansetron is given in 2 doses of 8 mg by mouth, one taken 30 to 60 minutes before chemotherapy, and one taken 8 hours after the first dose
- days 2 and 3: aprepitant 80 mg in the morning.

Administration in renal impairment. A study in 8 patients with severe renal impairment (24-hour creatinine clearance less than 30 mL/minute per 1.73 m^2) and 8 patients with end-stage renal disease requiring haemodialysis found that pharmacokinetic parameters of aprepitant were not sufficiently different from those in 16 matched controls to warrant dosage adjustment in renal impairment.[1] Licensed product information concurs with this.

1. Bergman AJ, *et al.* Effect of impaired renal function and haemodialysis on the pharmacokinetics of aprepitant. *Clin Pharmacokinet* 2005; **44:** 637–47.

Nausea and vomiting. Studies[1-8] and reviews.[9,10]

1. Campos D, *et al.* Prevention of cisplatin-induced emesis by the oral neurokinin-1 antagonist, MK-869, in combination with granisetron and dexamethasone or with dexamethasone alone. *J Clin Oncol* 2001; **19:** 1759–67.
2. Poli-Bigelli S, *et al.* Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting: results from a randomized, double-blind, placebo-controlled trial in Latin America. *Cancer* 2003; **97:** 3090–8.
3. de Wit R, *et al.* Addition of the oral NK antagonist aprepitant to standard antiemetics provides protection against nausea and vomiting during multiple cycles of cisplatin-based chemotherapy. *J Clin Oncol* 2003; **21:** 4105–11.
4. Hesketh PJ, *et al.* The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin—the Aprepitant Protocol 052 Study Group. *J Clin Oncol* 2003; **21:** 4112–19.
5. Warr DG, *et al.* Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. *J Clin Oncol* 2005; **23:** 2822–30. Correction. *ibid.*; 5851. [dosage error in abstract]
6. Warr DG, *et al.* The oral NK antagonist aprepitant for the prevention of acute and delayed chemotherapy-induced nausea and vomiting: pooled data from 2 randomised, double-blind, placebo controlled trials. *Eur J Cancer* 2005; **41:** 1278–85.
7. Herrstedt J, *et al.* Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and emesis over multiple cycles of moderately emetogenic chemotherapy. *Cancer* 2005; **104:** 1548–55.
8. Diemunsch P, *et al.* Preventing postoperative nausea and vomiting: post hoc analysis of pooled data from two randomized active-controlled trials of aprepitant. *Curr Med Res Opin* 2007; **23:** 2559–65.
9. Dando TM, Perry CM. Aprepitant: a review of its use in the prevention of chemotherapy-induced nausea and vomiting. *Drugs* 2004; **64:** 777–94.
10. Massaro AM, Lenz KL. Aprepitant: a novel antiemetic for chemotherapy-induced nausea and vomiting. *Ann Pharmacother* 2005; **39:** 77–85.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Emend; ***Austral.:*** Emend; ***Belg.:*** Emend; ***Braz.:*** Emend; ***Cz.:*** Emend; ***Denm.:*** Emend; ***Fin.:*** Emend; ***Fr.:*** Emend; ***Ger.:*** Emend; ***Gr.:*** Emend; ***Hong Kong:*** Emend; ***Hung.:*** Emend; ***Irl.:*** Emend; ***Ital.:*** Emend; ***Malaysia:*** Emend; ***Norw.:*** Emend; ***NZ:*** Emend; ***Port.:*** Emend; ***Rus.:*** Emend (Эмена); ***S.Afr.:*** Emend; ***Singapore:*** Emend; ***Spain:*** Emend; ***Swed.:*** Emend; ***Switz.:*** Emend; ***Thai.:*** Emend; ***UK:*** Emend; ***USA:*** Emend; ***Venez.:*** Emend.

Attapulgite

Atapulgit; Atapulgita.

Аттапульгит

CAS — 1337-76-4; 12174-11-7.

ATC — A07BC04.

ATC Vet — QA07BC04.

Pharmacopoeias. In *Br.*

Activated attapulgite is included in *Br.*, *It.*, and *US*. Colloidal activated attapulgite is included in *US*.

BP 2008 (Attapulgite). A purified native hydrated aluminium magnesium silicate essentially consisting of the clay mineral palygorskite. A light, cream or buff, very fine powder, free or almost free from gritty particles. A 5% suspension in water has a pH of 7.0 to 9.5.

BP 2008 (Activated Attapulgite). Attapulgite that has been carefully heated to increase its adsorptive capacity.

USP 31 (Activated Attapulgite). Processed native aluminium magnesium silicate which has been carefully heated. It is a cream-coloured, micronised, nonswelling powder, free from gritty particles. Insoluble in water.

USP 31 (Colloidal Activated Attapulgite). A native aluminium magnesium silicate that has been purified. It is a cream-coloured, micronised, nonswelling powder, free from gritty particles. Insoluble in water. A 10% suspension in water has a pH of 7.0 to 9.5.

◊ NOTE. Another native aluminium magnesium silicate is described on p.2141.

Profile

Attapulgite is highly adsorbent and is used in a wide range of products including fertilisers, pesticides, and pharmaceuticals. Activated attapulgite is an adsorbent antidiarrhoeal used as an adjunct in the management of diarrhoea (p.1694) in a daily dose of up to 9 g orally in divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Actapulgite; ***Canad.:*** Fowlers; Kaopectate; ***Fr.:*** Actapulgite; ***Hong Kong:*** Gastrosorb; ***Indon.:*** Biodiar; Enterogit; Kaotate; New Diatabs; Teradi; ***Malaysia:*** Entox-P†; ***Philipp.:*** Polymagma; ***Rus.:*** Neointestopan (Неоинтестопан); ***Switz.:*** Actapulgite; ***Thai.:*** Entox-P†; ***Turk.:*** Diyasorb; ***UAE:*** Kaptin II; ***USA:*** Diasorb; Kaopectate Advanced Formula†; Kaopectate Maximum Strength; Rheaban Maximum Strength†; ***Venez.:*** Streptomagma.

Multi-ingredient: *Arg.:* Enterobacticel; ***Austral.:*** Diareze; ***Braz.:*** Diazol; Dispeptrin; ***Chile:*** Diaren; Diarfin†; Entero Micinovo; Enterol; Liracol; Nifurat†; ***Fr.:*** Gastropulgite; Mucipulgite; ***Hong Kong:*** Enterocin Compound; ***Indon.:*** Andikap; Arcapec; Diagit; Entrogard; Fitodiar; Licopec; Molagit; Neo Diastop; Neo Entrostop; Neo Koniform; ***Ital.:*** Streptomagma; ***S.Afr.:*** Kantrexil; ***Switz.:*** Gastropulgite†; Mucipulgite†; ***Turk.:*** Streptomagma; ***UK:*** Diocalm Dual Action; ***Venez.:*** Micyn-2; Mycin-2†; Strediazin c Atapulguita†; Streptomagma.

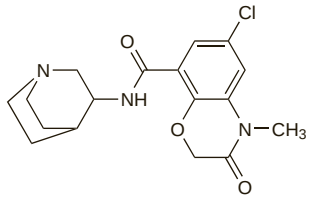
Azasetron Hydrochloride *(rINNM)*

Azasétron, Chlorhydrate d'; Azasetroni Hydrochloridum; Hidrocloruro de azasetrón; Nazasetron Hydrochloride; Y-25130. (±)-6-Chloro-3,4-dihydro-4-methyl-3-oxo-*N*-3-quinuclidinyl-2*H*-1,4-benzoxazine-8-carboxamide hydrochloride.

Азасетрона Гидрохлорид

$C_{17}H_{20}ClN_3O_3$,HCl = 386.3.

CAS — 123040-69-7 (azasetron); 141922-90-9 (azasetron hydrochloride).



(azasetron)

Profile

Azasetron is a 5-HT_3 antagonist with general properties similar to those of ondansetron (p.1756). It is used as an antiemetic in the management of nausea and vomiting induced by cytotoxic therapy. Azasetron hydrochloride is given in a usual dose of 10 mg once daily by mouth or intravenously.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Serotone†; ***Jpn:*** Serotone.

Balsalazide Sodium *(BANM, rINNM)*

Balsalazida sódica; Balsalazide Disodium *(USAN)*; Balsalazide Sodique; Balsalazine Disodium; BX-661A; Natrii Balsalazidum. 5-[4-(2-Carboxyethylcarbamoyl)phenylazo]salicylic acid, disodium salt, dihydrate.

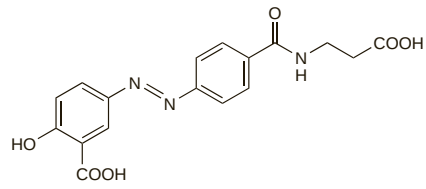
Натрий Балсалазид

$C_{17}H_{13}N_3Na_2O_6$,$2H_2O$ = 437.3.

CAS — 80573-04-2 (balsalazide); 150399-21-6 (balsalazide disodium dihydrate).

ATC — A07EC04.

ATC Vet — QA07EC04.



(balsalazide)

Adverse Effects and Precautions

As for Mesalazine, p.1745. If a blood dyscrasia is suspected treatment should be stopped immediately and a blood count performed. Patients or their carers should be told how to recognise signs of haematotoxicity and should be advised to seek immediate medical attention if symptoms such as fever, sore throat, mouth ulcers, bruising, or bleeding develop. Balsalazide should not be used in patients with severe hepatic impairment or moderate or severe renal impairment; care is required in those with lesser degrees of hepatic or renal impairment, and in asthma, bleeding disorders, or active peptic ulcer disease.

◊ Reviews.

1. Baker DE. Safety of balsalazide therapy in the treatment of inflammatory bowel disease. *Rev Gastroenterol Disord* 2005; **5:** 135–41.

Hypersensitivity. A case of acute pericarditis, cholestasis, and vasculitis resulting from hypersensitivity to balsalazide has been reported.[1] The authors noted similarities to mesalazine-associated pericarditis and lupus-like syndrome (see Effects on the Cardiovascular System, p.1745).

1. Adhiyaman V, *et al.* Hypersensitivity reaction to balsalazide. *BMJ* 2000; **320:** 613.

Pharmacokinetics

Very little of an oral dose of balsalazide is absorbed via the upper gastrointestinal tract, and almost the entire dose reaches its site of action in the colon intact. It is broken down by the colonic bacterial flora into 5-aminosalicylic acid (mesalazine), which is active, and 4-aminobenzoylalanine, which is considered to be an inert carrier. About 25% of the released mesalazine is absorbed and acetylated, as described under mesalazine (p.1746). A small proportion of 4-aminobenzoylalanine is absorbed and acetylated by first-pass metabolism through the liver. The acetylated metabolites are excreted in the urine.

Uses and Administration

Balsalazide consists of mesalazine linked to 4-aminobenzoylalanine via an azo bond. This bond is broken by colonic bacteria, releasing the active mesalazine (p.1746). Balsalazide sodium is given in the treatment of mild to moderate active ulcerative colitis (p.1697), in an oral dose of 2.25 g three times daily until remission or for up to 12 weeks. For maintenance of remission of ulcerative colitis a dose of 1.5 g twice daily is recommended, adjusted as necessary up to 6 g daily. For doses in children, see below.

◊ Reviews.

1. Muijsers RBR, Goa KL. Balsalazide: a review of its therapeutic use in mild-to-moderate ulcerative colitis. *Drugs* 2002; **62:** 1689–705.

Administration in children. Balsalazide sodium is not licensed in the UK for use in children under 18 years of age. However, the *BNFC* suggests that, in those aged 12 years and over, 2.25 g may be given orally three times daily for an acute attack of mild to moderate ulcerative colitis, until remission occurs, or