Alverine Citrate *(BANM, USAN, rINNM)*

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

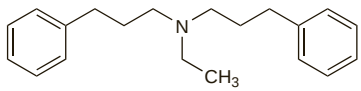
Альверина Цитрат

$C_{20}H_{27}N,C_6H_8O_7$ = 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†.

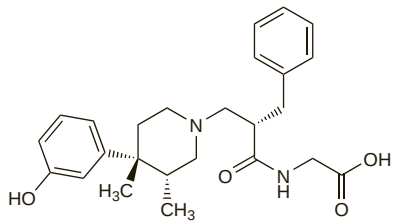
Alvimopan *(BAN, USAN, rINN)*

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.

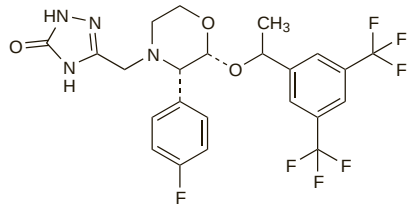
Апрепитант

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