Adverse Effects and Precautions

As for Sumatriptan, p.625.

Almotriptan should not be used in patients with severe hepatic impairment since clearance is likely to be markedly impaired, and should be given with caution, and in reduced doses, to patients with mild to moderate hepatic impairment. The dose of almotriptan should also be reduced in patients with severe renal impairment.

Patients with hypersensitivity to sulfonamides may theoretically exhibit a similar reaction to almotriptan.

Incidence of adverse effects. Results from studies involving more than 2500 patients with migraine suggested that adverse effects of almotriptan were infrequent.[1] The commonest adverse effects reported were dizziness, nausea and vomiting, headache, paraesthesia, fatigue, and drowsiness, all of which occurred in less than 3% of patients. The incidence of chest symptoms was 0.2% in 2 large phase III studies.

1. Dodick DW. Oral almotriptan in the treatment of migraine: safety and tolerability. *Headache* 2001; **41:** 449–55.

Interactions

As for Sumatriptan, p.626.

Pharmacokinetics

After oral doses, peak plasma-almotriptan concentrations are obtained in about 1 to 3 hours, with a bioavailability of about 70%. Protein binding is about 35%. Almotriptan is metabolised, mainly by monoamine oxidase type A to the inactive indole acetic acid derivative and to a lesser extent by cytochrome P450 isoenzymes CYP3A4 and CYP2D6 to the inactive gamma-aminobutyric acid derivative. More than 75% of an oral dose is excreted in the urine and the remainder in faeces. About 40 to 50% of the dose in the urine and 5% in the faeces is excreted as unchanged drug. The plasma elimination half-life is about 3.5 hours in healthy subjects, increasing to about 7 hours in severe renal impairment.

Distribution into milk has been found in studies in *rats*.

◊ References.

1. Jansat JM, *et al.* Absolute bioavailability, pharmacokinetics, and urinary excretion of the novel antimigraine agent almotriptan in healthy male volunteers. *J Clin Pharmacol* 2002; **42:** 1303–10.
2. McEnroe JD, Fleishaker JC. Clinical pharmacokinetics of almotriptan, a serotonin 5-HT receptor agonist for the treatment of migraine. *Clin Pharmacokinet* 2005; **44:** 237–46.

Uses and Administration

Almotriptan malate is a selective serotonin ($5\text{-}HT_1$) agonist with actions and uses similar to those of sumatriptan (p.627). It is used for the acute treatment of the headache phase of migraine attacks. It should not be used for prophylaxis. Almotriptan is given orally as the malate, and doses are expressed in terms of the base; almotriptan malate 8.75 mg is equivalent to about 6.25 mg of almotriptan.

The usual dose of almotriptan is 12.5 mg in the UK and 6.25 or 12.5 mg in the USA. If this is ineffective, a second dose should not be taken for the same attack. If symptoms recur within 24 hours after an initial response, a second dose may be taken after an interval of at least 2 hours. No more than 2 doses should be taken in a 24-hour period. For doses in hepatic and renal impairment see below.

◊ References.

1. Holm KJ, Spencer CM. Almotriptan. *CNS Drugs* 1999; **11:** 159–64.
2. Keam SJ, *et al.* Almotriptan: a review of its use in migraine. *Drugs* 2002; **62:** 387–414.

Administration in hepatic or renal impairment. In patients with hepatic or severe renal impairment, no more than 12.5 mg of almotriptan should be taken in 24 hours; a starting dose of 6.25 mg may be used. Almotriptan is contra-indicated in patients with severe hepatic disease.

Migraine. For comparison of the relative benefits of different triptans in migraine, see under Sumatriptan, p.627.

Further references.

1. Balbisi EA. Efficacy and safety of almotriptan malate for migraine. *Am J Health-Syst Pharm* 2002; **59:** 2184–93.
2. Dodick DW. A review of the clinical efficacy and tolerability of almotriptan in acute migraine. *Expert Opin Pharmacother* 2003; **4:** 1157–63.
3. Dowson AJ. Oral almotriptan: practical uses in the acute treatment of migraine. *Expert Rev Neurother* 2004; **4:** 339–48.
4. Mathew NT. Efficacy and tolerability of almotriptan in controlled clinical trials. *Eur Neurol* 2005; **53** (suppl 1): 29–33.
5. Pascual J. Efficacy and tolerability of almotriptan in postmarketing surveillance studies. *Eur Neurol* 2005; **53** (suppl 1): 34–40.
6. Dahlof CG, *et al.* Efficacy, speed of action and tolerability of almotriptan in the acute treatment of migraine: pooled individual patient data from four randomized, double-blind, placebo-controlled clinical trials. *Cephalalgia* 2006; **26:** 400–8.
7. Diener H-C. A review of recent clinical experience with almotriptan. *Drugs* 2006; **66** (suppl 3): 17–25.

Preparations

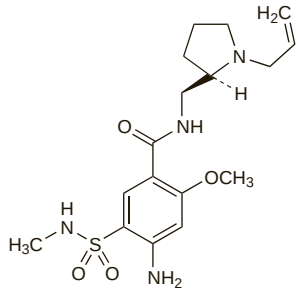
Proprietary Preparations (details are given in Part 3)
Belg.: Almogran; ***Canad.:*** Axert; ***Denm.:*** Almogran; ***Fin.:*** Almogran; ***Fr.:*** Almogran; ***Ger.:*** Almogran; ***Irl.:*** Almogran; ***Ital.:*** Almogran; Almotrex; ***Neth.:*** Almogran; ***Norw.:*** Almogran; ***Port.:*** Almogran; Amignul; ***Spain:*** Almogran; Amignul; ***Swed.:*** Almogran; ***UK:*** Almogran; ***USA:*** Axert.

Alpiropride *(rINN)*

Alpiroprida; Alpiropridum. (±)-*N*-[(1-Allyl-2-pyrrolidinyl)methyl]-4-amino-5-(methylsulfamoyl)-*o*-anisamide.

Альпироприд

$C_{17}H_{26}N_4O_4S$ = 382.5.
CAS — 81982-32-3.



Profile

Alpiropride is a dopamine antagonist that has been given orally for the treatment and prophylaxis of migraine.

Preparations

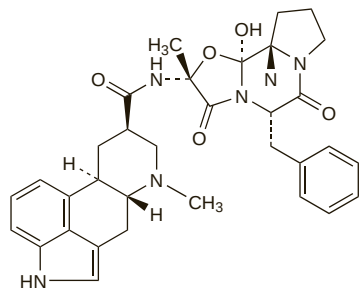
Proprietary Preparations (details are given in Part 3)
Port.: Rivistel†.

Dihydroergotamine *(BAN, rINN)*

Dihidroergotamina; Dihydroergotamiini; Dihydroergotamin; Dihydroergotaminum. (5′*S*,8*R*)-5′-Benzyl-9,10-dihydro-12′-hydroxy-2′-methyl-3′,6′,18-trioxoergotaman.

Дигидроэрготамин

$C_{33}H_{37}N_5O_5$ = 583.7.
CAS — 511-12-6.
ATC — N02CA01.
ATC Vet — QN02CA01.



Dihydroergotamine Mesilate *(BANM, rINNM)*

Dihidroergotamin-mezilát; Dihidroergotamino mesilatas; Dihydroergotamiinimesilaatti; Dihydroergotamine, mésilate de; Dihydroergotamine Mesylate *(USAN)*; Dihydroergotamine Methanesulphonate; Dihydroergotamini mesilas; Dihydroergotamin-mesilat; Dihydroergotamin-mesylát; Dihydroergotaminy mezylan; Mesilato de dihidroergotamina.

Дигидроэрготамина Мезилат

$C_{33}H_{37}N_5O_5,CH_4O_3S$ = 679.8.
CAS — 6190-39-2.
ATC — N02CA01.
ATC Vet — QN02CA01.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Dihydroergotamine Mesilate). Colourless crystals or a white or almost white crystalline powder. Slightly soluble in water and in alcohol; sparingly soluble in methyl alcohol. A 0.1% solution in water has a pH of 4.4 to 5.4. Protect from light.
USP 31 (Dihydroergotamine Mesylate). A white to slightly yellowish powder, or off-white to faintly red powder, having a faint odour. Soluble 1 in 125 of water, 1 in 90 of alcohol, 1 in 175 of chloroform, and 1 in 2600 of ether. pH of a 0.1% solution in water is between 4.4 and 5.4. Protect from light.

Dihydroergotamine Tartrate *(BANM, rINNM)*

Dihidroergotamino tartratas; Dihidroergotamin-tartarát; Dihydroergotamiinitartraatti; Dihydroergotamine, tartrate de; Dihydroergotamini tartras; Dihydroergotamin-tartarát; Dihydroergotamintartrat; Tartrato de dihidroergotamina.

Дигидроэрготамина Тартрат

$(C_{33}H_{37}N_5O_5)_2,C_4H_6O_6$ = 1317.4.
CAS — 5989-77-5.
ATC — N02CA01.
ATC Vet — QN02CA01.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Dihydroergotamine Tartrate). Colourless crystals or a white or almost white crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol. A 0.1% suspension in water has a pH of 4.0 to 5.5. Protect from light.

Adverse Effects and Treatment

As for Ergotamine Tartrate, p.620, although vasoconstriction may be less pronounced and the frequency of nausea and vomiting lower with dihydroergotamine mesilate than with ergotamine tartrate. Dihydroergotamine does not appear to produce physical dependence.

Effects on the cardiovascular system. There are conflicting reports on the risk of vasospasm in patients given dihydroergotamine with heparin for thromboembolism prophylaxis. Vasospastic or necrotic reactions have been reported on several occasions during such therapy.[1-4] In an Austrian study of 147 290 patients given drug prophylaxis for thromboembolism, complications attributable to ergotism were seen in 142 of 61 092 (0.23%) who received dihydroergotamine and heparin.[5] Others,[6] however, observed only 1 case of vasospasm in 5100 trauma patients (0.02%) given the combination. In 1989 the Swedish Adverse Drug Reactions Advisory Committee reported[7] that up to the end of September 1987 the manufacturer had received 201 reports of vasospastic reactions associated with the use of *Orstanorm* (dihydroergotamine + lidocaine) with heparin. Permanent damage occurred in 59% of these patients. Vasospastic reactions had occurred more frequently in patients who had undergone surgery for trauma and the prognosis for such patients was generally poorer than for others. Since the risk of permanent damage appeared to be related to treatment length the Committee recommended that this preparation should not be given for more than 7 days. The possibility of such reactions and the contra-indications of dihydroergotamine should be borne in mind when using this form of prophylaxis (see Venous Thromboembolism, under Uses, below).

1. van den Berg E, *et al.* Ergotism leading to threatened limb amputation or to death in two patients given heparin-dihydroergotamine prophylaxis. *Lancet* 1982; **i:** 955–6.
2. van den Berg E, *et al.* Vascular spasm during thromboembolism prophylaxis with heparin-dihydroergotamine. *Lancet* 1982; **ii:** 268–9.
3. Monreal M, *et al.* Skin and muscle necrosis during heparin-dihydroergotamine prophylaxis. *Lancet* 1984; **ii:** 820.
4. Kilroy RA, *et al.* Vascular spasm during heparin-dihydroergotamine prophylaxis. *Clin Pharm* 1987; **6:** 575–7.
5. Gatterer R. Ergotism as complication of thromboembolic prophylaxis with heparin and dihydroergotamine. *Lancet* 1986; **ii:** 638–9.
6. Schlag G, *et al.* Risk/benefit of heparin-dihydroergotamine thromboembolic prophylaxis. *Lancet* 1986; **ii:** 1465.
7. Swedish Adverse Drug Reaction Advisory Committee. Dihydroergotamine + lidocaine – vasospasm. *Bull Swed Adverse Drug React Advisory Committee* 1989; (54): 1.

Fibrosis. For reference to fibrosis associated with the administration of dihydroergotamine, see Methysergide Maleate, p.623.

Precautions

As for Ergotamine Tartrate, p.620.

Cardiovascular disorders. For specific contra-indications and precautions in cardiovascular disorders, see under Ergotamine, p.621.

Porphyria. Dihydroergotamine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for Ergotamine (p.621).

Use with other vasoconstrictive drugs, including supplementary antimigraine treatment with ergotamine or sumatriptan, should be avoided.