Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Arwin.

Angiotensinamide *(BAN, rINN)*

Angiotensiiniamidi; Angiotensin Amide *(USAN)*; Angiotensinamid; Angiotensinamida; Angiotensinamidum; NSC-107678. Asn-Arg-Val-Tyr-Val-His-Pro-Phe; [1-Asparagine,5-valine]angiotensin II.

Ангиотенсинамид

$C_{49}H_{70}N_{14}O_{11}$ = 1031.2.
CAS — 11128-99-7 (angiotensin II); 53-73-6 (angiotensinamide).
ATC — C01CX06.
ATC Vet — QC01CX06.

Profile

Angiotensinamide is a vasopressor related to the naturally occurring peptide angiotensin II. It increases the peripheral resistance mainly in cutaneous, splanchnic, and renal blood vessels. The increased blood pressure is accompanied by a reflex reduction in heart rate, and cardiac output may also be reduced.

Angiotensinamide has been used in the treatment of hypotension associated with shock. It has also been given in the management of overdosage of ACE inhibitors, when conventional therapy has been ineffective.

Angiotensinamide should not be given to patients being treated with an MAOI or within 14 days of stopping such treatment as a hypertensive crisis may be precipitated.

◊ References.

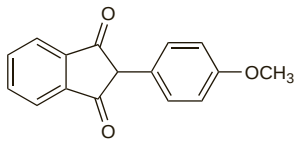
1. Jackson T, *et al*. Enalapril overdose treated with angiotensin infusion. *Lancet* 1993; **341:** 703.
2. Newby DE, *et al.* Enalapril overdose and the corrective effect of intravenous angiotensin II. *Br J Clin Pharmacol* 1995; **40:** 103–4.
3. Yunge M, Petros A. Angiotensin for septic shock unresponsive to noradrenaline. *Arch Dis Child* 2000; **82:** 388–9.

Anisindione *(BAN, rINN)*

Anisindiona; Anisindionum. 2-(4-Methoxyphenyl)indan-1,3-dione.

Анизиндион

$C_{16}H_{12}O_3$ = 252.3.
CAS — 117-37-3.



Profile

Anisindione is an oral indanedione anticoagulant with actions similar to those of warfarin (p.1425). It has been used in the management of thromboembolic disorders (p.1187) but, as the indanediones are generally more toxic than warfarin (see Phenindione, p.1369), its use is limited.

Use of anisindione may colour the urine pink or orange.

Anistreplase *(BAN, USAN, rINN)*

Anisoylated Plasminogen Streptokinase Activator Complex; Anistreplaasi; Anistreplas; Anistreplasa; Anistreplasum; APSAC; BRL-26921. *p*-Anisoylated (human) lys-plasminogen streptokinase activator complex (1:1).

Анистреплаза

CAS — 81669-57-0.
ATC — B01AD03.
ATC Vet — QB01AD03.

Storage. The manufacturer recommends that anistreplase should be stored at 2° to 8°.

Adverse Effects, Treatment, and Precautions

As for Streptokinase, p.1402. Like streptokinase, anistreplase appears to be antigenic and may be neutralised by streptokinase antibodies.

Back pain. For references to back pain associated with anistreplase infusion, see under Streptokinase, p.1402.

Interactions

As for Streptokinase, p.1404.

Pharmacokinetics

Anistreplase is reported to be cleared from plasma at about half the rate of streptokinase and has a fibrinolytic half-life of about 90 minutes. It is metabolised to the plasminogen-streptokinase complex at a steady rate.

◊ References.

1. Gemmill JD, *et al*. A comparison of the pharmacokinetic properties of streptokinase and anistreplase in acute myocardial infarction. *Br J Clin Pharmacol* 1991; **31:** 143–7.

Uses and Administration

Anistreplase is a thrombolytic drug. It consists of a complex of the lys-form of plasminogen and streptokinase with the addition of a *p*-anisoyl group. After intravenous injection the anisoyl group undergoes deacylation at a steady rate to release the active complex which converts plasminogen to plasmin, a proteolytic enzyme that has fibrinolytic effects. The mechanisms of fibrinolysis are discussed further under Haemostasis and Fibrinolysis on p.1045.

Anistreplase is used similarly to streptokinase (p.1404) in the treatment of acute myocardial infarction (p.1175). It is given as a single intravenous injection in a dose of 30 units over 5 minutes, as soon as possible after the onset of symptoms.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Eminase; ***Belg.:*** Eminase†; ***Ger.:*** Eminase; ***Neth.:*** Eminase†.

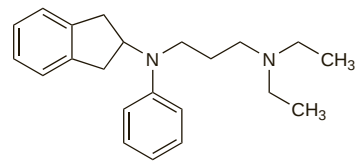
Multi-ingredient: ***Israel:*** Eminase†.

Aprindine Hydrochloride *(BANM, USAN, rINNM)*

AC-1802; Aprindine, Chlorhydrate d'; Aprindini Hydrochloridum; Compound 83846; Compound 99170 (aprindine); Hidrocloruro de aprindina. *N*-(3-Diethylaminopropyl)-*N*-indan-2-ylaniline hydrochloride; *NN*-Diethyl-*N'*-indan-2-yl-*N'*-phenyltrimethylenediamine hydrochloride.

Априндина Гидрохлорид

$C_{22}H_{30}N_2$,HCl = 358.9.
CAS — 37640-71-4 (aprindine); 33237-74-0 (aprindine hydrochloride).
ATC — C01BB04.
ATC Vet — QC01BB04.



(aprindine)

Adverse Effects and Precautions

Adverse effects of aprindine are usually dose-related and most commonly affect the CNS. They include tremor, vertigo, ataxia, diplopia, memory impairment, hallucinations, and convulsions. Gastrointestinal effects include nausea, vomiting, and bloating. There have been reports of agranulocytosis, including fatalities. Hepatitis and cholestatic jaundice have occasionally been reported; blood and liver function tests should be performed during treatment.

Aprindine is contra-indicated in patients with advanced heart failure or severe conduction disturbances. Some licensed product information has recommended that aprindine should not be used in patients with parkinsonism or convulsive disorders. It should be used with caution in patients with bradycardia, hypotension, and hepatic or renal impairment.

Interactions

Antiarrhythmics. Steady-state plasma-aprindine concentrations increased in 2 patients after starting *amiodarone* and this coincided with the appearance of adverse effects.[1]

1. Southworth W, *et al*. Possible amiodarone-aprindine interaction. *Am Heart J* 1982; **104:** 323.

Pharmacokinetics

Aprindine is readily absorbed from the gastrointestinal tract. It has a long plasma half-life, usually between 20 and 27 hours, and is about 85 to 95% bound to plasma proteins. It is excreted in the urine and the bile.

Uses and Administration

Aprindine is a class Ib antiarrhythmic (p.1153) used in the management of ventricular and supraventricular arrhythmias (p.1160).

Aprindine is given as the hydrochloride in usual oral maintenance doses of 50 to 100 mg daily. Initial doses of 150 to 200 mg daily, in divided doses, may be given under strict surveillance for the first 2 to 3 days; up to 300 mg may be given on the first day if necessary. Therapy should be monitored by ECG during initial stabilisation of the dose and intermittently thereafter. Aprindine has also been given intravenously.

Preparations

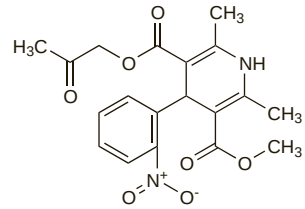
Proprietary Preparations (details are given in Part 3)
Belg.: Fiboran†; ***Fr.:*** Fiboran†; ***Neth.:*** Fiboran.

Aranidipine *(rINN)*

Aranidipino; Aranidipinum; MPC-1304. (±)-Acetonyl methyl 1,4-dihydro-2,6-dimethyl-4-(*o*-nitrophenyl)-3,5-pyridinedicarboxylate.

Аранидипин

$C_{19}H_{20}N_2O_7$ = 388.4.
CAS — 86780-90-7.



Profile

Aranidipine is a dihydropyridine calcium-channel blocker used in the management of hypertension.

Preparations

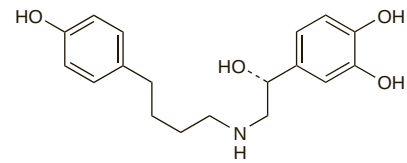
Proprietary Preparations (details are given in Part 3)
Jpn: Bec; Flaspas†; Sapresta.

Arbutamine Hydrochloride *(BANM, USAN, rINNM)* ⊗

Arbutamine, Chlorhydrate d'; Arbutamini Hydrochloridum; GP-2-121-3 (arbutamine or arbutamine hydrochloride); Hidrocloruro de arbutamina. (*R*)-4-(1-Hydroxy-2-[4-(4-hydroxyphenyl)-butylamino]ethyl)pyrocatechol hydrochloride.

Арбутамина Гидрохлорид

$C_{18}H_{23}NO_4$,HCl = 353.8.
CAS — 128470-16-6 (arbutamine); 125251-66-3 (arbutamine hydrochloride).
ATC — C01CA22.
ATC Vet — QC01CA22.



(arbutamine)

Profile

Arbutamine hydrochloride is a sympathomimetic (p.1407) with beta-agonist properties and like dobutamine (p.1272) has been used for cardiac stress testing in patients unable to exercise.

◊ References.

1. Anonymous. Arbutamine for stress testing. *Med Lett Drugs Ther* 1998; **40:** 19–20.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Genesa†.

Ardeparin Sodium *(USAN, rINN)*

Ardeparina sódica; Ardéparine Sodique; Ardeparinum Natricum; Wy-90493-RD.

Ардепарин Натрий

CAS — 9041-08-1.

Description. Ardeparin sodium is prepared by peroxide degradation of heparin obtained from the intestinal mucosa of pigs. The end chain structure appears to be the same as the starting material with no unusual sugar residues present. The molecular weight of 98% of the components is between 2000 and 15 000 and the average molecular weight is about 5500 to 6500. The degree of sulfation is about 2.7 per disaccharide unit.

Profile

Ardeparin sodium is a low-molecular-weight heparin (p.1329) with anticoagulant activity that has been used for the prevention of postoperative venous thromboembolism.

Argatroban *(BAN, USAN, rINN)*

Argatrobanum; Argipidine; DK-7419; GN-1600; MCI-9038; MD-805. (2*R*,4*R*)-4-Methyl-1-[(*S*)-N^2-{[(*RS*)-1,2,3,4-tetrahydro-3-methyl-8-quinolyl]sulfonyl}arginyl]pipecolic acid.

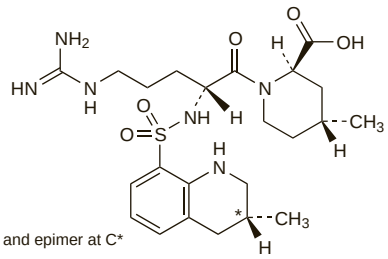
Аргатробан

$C_{23}H_{36}N_6O_5S$ = 508.6.

CAS — 74863-84-6 (anhydrous argatroban); 141396-28-3 (argatroban monohydrate).

ATC — B01AE03.

ATC Vet — QB01AE03.



and epimer at C*

Incompatibility. Trace evidence of precipitation was seen immediately after mixing solutions of argatroban and amiodarone.[1] No visual incompatibility was noted for solutions of argatroban with furosemide, nesiritide, sodium nitroprusside, or a total parenteral nutrition solution, but changes in pH occurred over 24 hours, suggesting such mixtures should be used with caution.[1]

1. Honisko ME, *et al.* Compatibility of argatroban with selected cardiovascular agents. *Am J Health-Syst Pharm* 2004; **61:** 2415–18.

Adverse Effects and Precautions

As for Lepirudin, p.1323.

If argatroban and warfarin are given together there is an effect on the measurement of the INR values. The manufacturer provides guidelines for interpreting the INR during the change from combined therapy to warfarin alone.

Administration in the critically ill. Four critically ill patients became excessively anticoagulated[1] when treatment with argatroban was started after cardiac surgery, despite use of only the recommended doses or lower. All four had relatively normal hepatic function. Clearance of the drug appeared to be prolonged after it was stopped. In a patient[2] who had no significant direct hepatic dysfunction but severe hepatic congestion secondary to acute renal failure, the effect of argatroban was prolonged and reduction in dose was necessary. Haemodialysis had little or no effect on clearance. Further cases of excessive anticoagulation have been reported in patients with multiple organ failure,[3] and in an elderly patient with multiple comorbidities.[4] Patients developing heparin-induced thrombocytopenia after cardiac surgery may also be more sensitive to argatroban, and an initial dose of 500 nanograms/kg per minute has been suggested.[5]

1. Reichert MG, *et al.* Excessive argatroban anticoagulation for heparin-induced thrombocytopenia. *Ann Pharmacother* 2003; **37:** 652–4.
2. de Denus S, Spinler SA. Decreased argatroban clearance unaffected by hemodialysis in anasarca. *Ann Pharmacother* 2003; **37:** 1237–40.
3. Beiderlinden M, *et al.* Argatroban anticoagulation in critically ill patients. *Ann Pharmacother* 2007; **41:** 749–54.
4. Kubiak DW, *et al.* Extensive prolongation of aPTT with argatroban in an elderly patient with improving renal function, normal hepatic enzymes, and metastatic lung cancer. *Ann Pharmacother* 2005; **39:** 1119–23.
5. Hoffman WD, *et al.* Reduced argatroban doses after coronary artery bypass graft surgery. *Ann Pharmacother* 2008; **42:** 309–16.

Overdosage. A critically ill patient receiving low-dose continuous intravenous argatroban for thromboembolism prophylaxis was mistakenly given an additional infusion of 125 mg of argatroban over 1 hour (26.1 micrograms/kg per minute).[1] He was given repeated doses of fresh frozen plasma and no bleeding complications occurred, but the prothrombin time remained prolonged for over 48 hours. Although the total dose given was comparable to doses used in other indications, critically ill patients may be particularly sensitive to the effects of argatroban (see above).

1. Yee AJ, Kuter DJ. Successful recovery after an overdose of argatroban. *Ann Pharmacother* 2006; **40:** 336–9.

Interactions

As for Lepirudin, p.1323.

Warfarin. Although caution is necessary in interpreting the INR when argatroban and warfarin are given together (see Adverse Effects and Precautions, above), a study in healthy subjects[1] showed no pharmacokinetic interaction.

1. Brown PM, Hursting MJ. Lack of pharmacokinetic interactions between argatroban and warfarin. *Am J Health-Syst Pharm* 2002; **59:** 2078–83.

Pharmacokinetics

Argatroban is about 54% bound to plasma proteins. Metabolism, mainly hydroxylation and aromatisation, takes place in the liver, with the main metabolite having weak anticoagulant activity. Anticoagulant effects are seen immediately upon starting infusion; steady-state concentrations occur within 1 to 3 hours and are maintained until the infusion is stopped or the dose adjusted. The terminal elimination half-life of argatroban is between 39 and 51 minutes. It is excreted primarily in the faeces, via the bile as metabolites and as unchanged drug. About 16% of a dose is excreted unchanged in the urine, and at least 14% unchanged in faeces.

Uses and Administration

Argatroban is a synthetic direct thrombin inhibitor (see Lepirudin, p.1323) with anticoagulant and antiplatelet activity. It is used for the treatment and prophylaxis of thromboembolism in patients with heparin-induced thrombocytopenia (see Effects on the Blood under Heparin, p.1302), and as an adjunct in patients undergoing percutaneous coronary interventions (see Reperfusion and Revascularisation Procedures, p.1181) who have or are at risk of heparin-induced thrombocytopenia. It has also been used in other thromboembolic disorders.

In the management of heparin-induced thrombocytopenia, argatroban is given by intravenous infusion in an initial dose of 2 micrograms/kg per minute, adjusted according to the activated partial thromboplastin time (APTT), to a maximum dose of 10 micrograms/kg per minute.

In percutaneous coronary interventions in patients at risk of or with heparin-induced thrombocytopenia, argatroban is given by intravenous infusion in an initial dose of 25 micrograms/kg per minute, and an intravenous injection of 350 micrograms/kg is given simultaneously over 3 to 5 minutes. Close monitoring of the activated clotting time (ACT) is required. If necessary, additional intravenous bolus doses of 150 micrograms/kg may be given, and the infusion rate adjusted to between 15 and 40 micrograms/kg per minute.

Doses should be reduced in patients with hepatic impairment (see below).

◊ References.

1. Kondo LM, *et al.* Argatroban for prevention and treatment of thromboembolism in heparin-induced thrombocytopenia. *Ann Pharmacother* 2001; **35:** 440–51.
2. McKeage K, Plosker GL. Argatroban. *Drugs* 2001; **61:** 515–22.
3. Verme-Gibboney CN, Hursting MJ. Argatroban dosing in patients with heparin-induced thrombocytopenia. *Ann Pharmacother* 2003; **37:** 970–5.
4. Lewis BE, *et al.* Effects of argatroban therapy, demographic variables, and platelet count on thrombotic risks in heparin-induced thrombocytopenia. *Chest* 2006; **129:** 1407–16.
5. Martin ME, *et al.* Argatroban for anticoagulation during cardiac surgery. *Eur J Haematol* 2007; **78:** 161–6.
6. Bartholomew JR, *et al.* Argatroban anticoagulation for heparin-induced thrombocytopenia in elderly patients. *Drugs Aging* 2007; **24:** 489–99.
7. Beiderlinden M, *et al.* Argatroban in extracorporeal membrane oxygenation. *Artif Organs* 2007; **31:** 461–5.
8. Boggio LN, Oza VM. Argatroban use in heparin-induced thrombocytopenia. *Expert Opin Pharmacother* 2008; **9:** 1963–7.

Administration in hepatic impairment. In patients with heparin-induced thrombocytopenia with hepatic impairment the initial dose of argatroban should be reduced.[1] US licensed product information recommends an initial dose of 500 nanograms/kg per minute in moderate hepatic impairment. Reversal of anticoagulant effects after stopping argatroban may take more than 4 hours, due to decreased clearance and increased elimination half-life. High doses of argatroban should not be used in patients with significant hepatic impairment undergoing percutaneous coronary interventions.

1. Levine RL, *et al.* Argatroban therapy in heparin-induced thrombocytopenia with hepatic dysfunction. *Chest* 2006; **129:** 1167–75.

Administration in renal impairment. Argatroban is not significantly excreted by the kidneys and dosage adjustment is not usually required in renal impairment, although excessive anticoagulation has been reported in critically ill patients, including some with compromised renal function (see Administration in the Critically Ill under Adverse Effects, above). Argatroban has been successfully used for anticoagulation in patients undergoing chronic haemodialysis who developed thrombocytopenia with heparin.[1] Argatroban was not significantly removed by dialysis and no dosage adjustment was required. The use of argatroban in patients with renal impairment has been reviewed.[2]

1. Tang IY, *et al.* Argatroban and renal replacement therapy in patients with heparin-induced thrombocytopenia. *Ann Pharmacother* 2005; **39:** 231–6.
2. Hursting MJ, Murray PT. Argatroban anticoagulation in renal dysfunction: a literature analysis. *Nephron Clin Pract* 2008; **109:** c80–c94.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Novastan; ***Neth.:*** Arganova; ***Swed.:*** Novastan; ***USA:*** Argatroban.

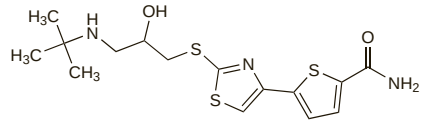
Arotinolol Hydrochloride *(rINNM)* ⊗

Arotinolol, Chlorhydrate d'; Arotinololi Hydrochloridum; Hidrocloruro de arotinolol; S-596. (±)-5-[2-{[3-(*tert*-Butylamino)-2-hydroxypropyl]thio}-4-thiazolyl]-2-thiophenecarboxamide hydrochloride.

Аротинолола Гидрохлорид

$C_{15}H_{21}N_3O_2S_3$,HCl = 408.0.

CAS — 68377-92-4 (arotinolol); 68377-91-3 (arotinolol hydrochloride).



(arotinolol)

Pharmacopoeias. In *Jpn.*

Profile

Arotinolol is a non-cardioselective beta blocker (p.1225); it also has $alpha_1$-blocking activity. It is used as the hydrochloride in the management of hypertension (p.1171), angina pectoris (p.1157), cardiac arrhythmias (p.1160), and essential tremor (p.1231). The usual oral dose is 20 mg daily in 2 divided doses although up to 30 mg daily may be given. The initial dose for essential tremor is 10 mg daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Almarl.

Atenolol *(BAN, USAN, rINN)* ⊗

Aténolol; Atenololi; Atenololis; Atenololum; ICI-66082. 2-{*p*-[2-Hydroxy-3-(isopropylamino)propoxy]phenyl}acetamide.

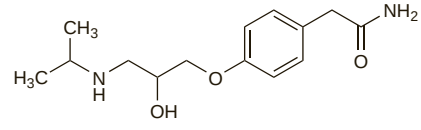
Атенолол

$C_{14}H_{22}N_2O_3$ = 266.3.

CAS — 29122-68-7; 60966-51-0.

ATC — C07AB03.

ATC Vet — QC07AB03.



NOTE. Compounded preparations of atenolol may be represented by the following names:

- Co-tenidone (*BAN*)—atenolol 4 parts and chlortalidone 1 part (w/w)
- Co-tenidone (*PEN*)—atenolol and chlortalidone.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Atenolol). A white or almost white powder. Sparingly soluble in water; soluble in dehydrated alcohol; slightly soluble in dichloromethane.
USP 31 (Atenolol). White or practically white, odourless powder. Slightly soluble in water and in isopropyl alcohol; sparingly soluble in alcohol; freely soluble in methyl alcohol.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.