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.

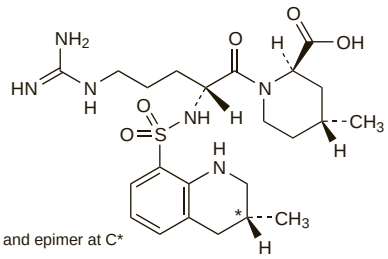
Аргатробан

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

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

ATC — B01AE03.

ATC Vet — QB01AE03.



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.

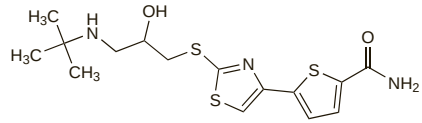
Arotinolol Hydrochloride *(rINNM)* ⊗

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.

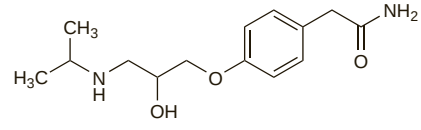
Атенолол

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