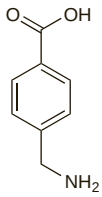
Aminomethylbenzoic Acid

Aminometilbenzoico, ácido; PAMBA. 4-Aminomethylbenzoic acid.

$C_8H_9NO_2$ = 151.2.
CAS — 56-91-7.
ATC — B02AA03.
ATC Vet — QB02AA03.



Profile

Aminomethylbenzoic acid is an antifibrinolytic with actions and uses similar to those of tranexamic acid (p.1080). It is given orally in typical doses of 300 mg to 1 g daily, in 3 or 4 divided doses; it is also given by intramuscular injection, or intravenously by slow injection or infusion.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Gumbix†; ***Cz.:*** Gumbix†; Pamba; ***Ger.:*** Gumbix; Pamba.

Ancestim *(USAN, rINN)*

Ancestimum; r-metHuSCF; SCF; Stem Cell Factor. *N*-L-Methionyl-1–165-haematopoietic cell growth factor KL (human clone V19.8:hSCF162), dimer.

Анцестим
CAS — 163545-26-4.
ATC — L03AA12.
ATC Vet — QL03AA12.

Adverse Effects and Precautions

Injection site reactions commonly occur with the use of ancestim. Other skin reactions, including pruritus, rash, and urticaria, are less frequent. Systemic hypersensitivity reactions are also common and may be life-threatening. Premedication with antihistamines (both H_1- and H_2-antagonists) and an inhaled beta$_2$ agonist bronchodilator should be used, and the patient observed for at least an hour after ancestim is given. Tachycardia and respiratory symptoms including pharyngitis, dyspnoea, and cough, have also been reported.

Ancestim should not be given in the period from 24 hours before to 24 hours after a dose of cytotoxic chemotherapy or radiotherapy.

Uses and Administration

Ancestim is a recombinant human stem cell factor. It is used with filgrastim (p.1070) to mobilise peripheral blood progenitor cells that are to be collected by apheresis harvest and used for autologous transplantation. The dose of ancestim is 20 micrograms/kg daily by subcutaneous injection; the injections of ancestim and filgrastim must be given at separate sites.

◊ References.

1. Chin-Yee IH, *et al.* Optimising parameters for peripheral blood leukapheresis after r-metHuG-CSF (filgrastim) and r-metHuSCF (ancestim) in patients with multiple myeloma: a temporal analysis of CD34(+) absolute counts and subsets. *Bone Marrow Transplant* 2002; **30:** 851–60.
2. Prosper F, *et al.* Mobilization of peripheral blood progenitor cells with a combination of cyclophosphamide, r-metHuSCF and filgrastim in patients with breast cancer previously treated with chemotherapy. *Leukemia* 2003; **17:** 437–41.
3. To LB, *et al.* Successful mobilization of peripheral blood stem cells after addition of ancestim (stem cell factor) in patients who had failed a prior mobilization with filgrastim (granulocyte colony-stimulating factor) alone or with chemotherapy plus filgrastim. *Bone Marrow Transplant* 2003; **31:** 371–8.
4. da Silva MG, *et al.* Ancestim (recombinant human stem cell factor, SCF) in association with filgrastim does not enhance chemotherapy and/or growth factor-induced peripheral blood progenitor cell (PBPC) mobilization in patients with a prior insufficient PBPC collection. *Bone Marrow Transplant* 2004; **34:** 683–91.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Stemgen; ***Canad.:*** Stemgen; ***NZ:*** Stemgen.

Antithrombin III *(BAN, rINN)*

Antithrombin III Human; Antithrombine III; Antithrombinum III; Antitrombiini III; Antitrombin III; Antitrombina III; Antitrombina III humana; Antytrombina III; AT-III; Cofactor I de la heparina; Heparin Cofactor; Heparin Cofactor I; Major Antithrombin.

Антитромбин III
CAS — 52014-67-2.
ATC — B01AB02.
ATC Vet — QB01AB02.

Pharmacopoeias. Many pharmacopoeias have monographs, including *Eur.* (see p.vii) and *US*.

Ph. Eur. 6.2 (Human Antithrombin III Concentrate; Antithrombinum III Humanum Densatum). A preparation of a glycoprotein fraction obtained from human plasma that inactivates thrombin in the presence of an excess of heparin. The plasma is obtained from healthy donors and is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. The method of preparation includes a step or steps that have been shown to remove or to inactivate known agents of infection. The antithrombin III concentrate is passed through a bacteria-retentive filter, distributed into sterile containers, and immediately frozen. The preparation is freeze-dried and the containers sealed under vacuum or in an atmosphere of inert gas. No antimicrobial preservative is added but a suitable stabiliser (such as albumin) is permitted. When reconstituted in the volume of solvent stated on the label, the resulting solution contains not less than 25 international units of antithrombin III per mL.
A white or almost white, hygroscopic, friable solid or powder. Store in airtight containers. Protect from light.

USP 31 (Antithrombin III Human). A glycoprotein, which is the major inhibitor of thrombin and other activated clotting factors, including factors IX, X, XI, and XII, and the cofactor through which heparin exerts its effect. It is obtained from human plasma of healthy donors who must, as far as can be ascertained, be free from detectable agents of infection transmissible by transfusion of blood or blood derivatives. The method of manufacturing includes steps that have been shown to remove or inactivate known agents of infection. The antithrombin III concentrate is passed through a bacteria-retentive filter, filled aseptically into its final, sterile containers, and immediately frozen. It is then freeze-dried, and the containers are closed under vacuum. No antimicrobial preservative is added at any stage of production. When reconstituted in the recommended volume of diluent, the pH is between 6.0 and 7.5, and the potency is not less than 25 USP units of antithrombin III per mL.
Store at a temperature of 2° to 8°, excursions permitted up to 25°. Protect from light.

Antithrombin Alfa *(USAN, rINN)*

Antithrombine Alfa; Antithrombinum Alfa; Antitrombina alfa; Human Antithrombin III from the milk of transgenic goats (glycoform alfa); Recombinant Human Antithrombin.

Антитромбин Альфа
CAS — 84720-88-7.

Units

The potency of antithrombin III is expressed in international units and preparations may be assayed using the second International Standard for antithrombin concentrate (1997); each ampoule contains 4.7 international units of functional activity and 5.1 international units of antigenic activity.

One USP unit is described as the amount of antithrombin III that forms a complex with 1 unit of thrombin at 25° in the presence of heparin at a pH of 8.4. Since assays of antithrombin III are carried out at 37°, it is unclear whether USP units and international units are precisely equivalent, but in practice US preparations, like those elsewhere, appear to have their potency defined in international units.

The potency of antithrombin alfa is also expressed in international units.

Adverse Effects and Precautions

Adverse effects of antithrombin III include flushing, headache, dizziness, chest tightness, nausea, a foul taste in the mouth, chills, and cramps. These can be controlled by slowing or stopping the infusion. Allergic reactions occur rarely.

Human plasma-derived antithrombin III preparations carry a risk of viral transmission. Manufacturing processes, including heating to about 60°, have reduced the risk of transmitting some viral infections. Antithrombin alfa is produced in the milk of transgenic goats, and should not be used in patients who are hypersensitive to goat proteins or goat milk components.

Uses and Administration

Antithrombin III is a protein in plasma; it is the major endogenous inhibitor of thrombin and other activated clotting factors including factors IX, X, XI, and XII (p.1045), and is the cofactor through which heparin (p.1303) exerts its effect. Genetic and acquired deficiency of antithrombin III occurs and is associated with susceptibility to thromboembolic disorders.

Human plasma-derived antithrombin III is given intravenously to patients with antithrombin III deficiency in the treatment of thromboembolism and for prophylaxis associated with surgical and obstetric procedures. The aim of therapy is to restore plasma-antithrombin III concentrations to at least 80% of normal. The dose, frequency, and duration of therapy are individualised for each patient taking into account the patient's pretreatment concentration and presence of active coagulation. A usual initial dose is about 30 to 50 international units/kg.

Antithrombin alfa is used similarly in the prophylaxis of venous thromboembolism in surgical patients with congenital antithrombin III deficiency. The dose is individualised, but a usual initial dose is about 20 to 25 international units/kg given as an intravenous infusion over 15 minutes, followed by a maintenance infusion of about 4 to 5 international units/kg per hour.

◊ References.

1. Bucur SZ, *et al.* Uses of antithrombin III concentrate in congenital and acquired deficiency states. *Transfusion* 1998; **38:** 481–98.
2. Roemisch J, *et al.* Antithrombin: a new look at the actions of a serine protease inhibitor. *Blood Coag Fibrinol* 2002; **13:** 657–70.
3. Konkle BA, *et al.* Use of recombinant human antithrombin in patients with congenital antithrombin deficiency undergoing surgical procedures. *Transfusion* 2003; **43:** 390–4.

Septicaemia. Antithrombin III has been used in septicaemia (p.190) in an attempt to manage the pro-coagulant state that occurs. Initial small studies reported a reduction in mortality[1] but a large controlled study[2] (KyberSept) found that treatment with antithrombin III had no effect on 28-day mortality. A further small observational study and meta-analysis also found no benefit from the use of antithrombin III in septicaemia.[3] These studies had used antithrombin III for less than 7 days, and a small study[4] in surgical patients with septicaemia found that 14 days of treatment with antithrombin III did improve measures of coagulation and fibrinolysis, the changes being most evident in the second week of therapy. However, the study was not large enough to test effects on mortality. Subsequent analysis of data from the KyberSept study appeared to show that 28-day mortality was in fact reduced in patients who had not been given heparin as well as antithrombin III;[5] combined use increased the risk of bleeding and apparently decreased the benefits of treatment with antithrombin III.

1. Eisele B, *et al.* Antithrombin III in patients with severe sepsis: a randomized, placebo-controlled, double-blind multicenter trial plus a meta-analysis on all randomized, placebo-controlled, double-blind trials with antithrombin III in severe sepsis. *Intensive Care Med* 1998; **24:** 663–72.
2. Warren BL, *et al.* KyberSept Trial Study Group. High-dose antithrombin III in severe sepsis: a randomized controlled trial. *JAMA* 2001; **286:** 1869–78. Correction. *ibid.* 2002; **287:** 192.
3. Messori A, *et al.* Antithrombin III in patients admitted to intensive care units: a multicenter observational study. *Crit Care* 2002; **6:** 447–51.
4. Hoffmann JN, *et al.* Effect of long-term and high-dose antithrombin supplementation on coagulation and fibrinolysis in patients with severe sepsis. *Crit Care Med* 2004; **32:** 1851–9.
5. Hoffmann JN, *et al.* The KyberSept Investigators. Benefit/risk profile of high-dose antithrombin in patients with severe sepsis treated with and without concomitant heparin. *Thromb Haemost* 2006; **95:** 850–6.

Veno-occlusive disease. There is some evidence[1] from case reports and small studies that antithrombin III may have a beneficial effect on veno-occlusive disease associated with haematopoietic stem cell transplantation (p.1811).

1. Ibrahim RB, *et al.* Anti-thrombin III in the management of hematopoietic stem-cell transplantation–associated toxicity. *Ann Pharmacother* 2004; **38:** 1053–9.

Preparations

Ph. Eur.: Human Antithrombin III Concentrate;
USP 31: Antithrombin III Human.

Proprietary Preparations (details are given in Part 3)
Arg.: Kybernin P; ***Austral.:*** Thrombotrol-VF; ***Austria:*** Atenativ; Kybernin P; Thrombhibin; ***Braz.:*** Kybernin P; ***Canad.:*** Thrombate; ***Cz.:*** Anbinex; ATryn; Kybernin P; ***Denm.:*** Atenativ; ***Fin.:*** Atenativ; ***Fr.:*** Aclotine; ***Ger.:*** Anbinex; AT III; Atenativ; Kybernin; ***Gr.:*** Atenativ; Kybernin P; ***Hung.:*** Atenativ; Kybernin P; ***Indon.:*** Kybernin P; ***Ital.:*** Anbin; Atenativ; Kybernin P; ***Jpn:*** Neuart; ***Mex.:*** Atend; Octatit; ***Neth.:*** Atenativ; ***Norw.:*** Atenativ; ***NZ:*** Thrombotrol-VF; ***Port.:*** Atenativ; ATryn; ***Spain:*** Anbinex; Atenativ; Kybernin P; ***Swed.:*** Atenativ; ***Switz.:*** Atenativ; Kybernin; ***Turk.:*** Kybernin P; ***UK:*** ATryn; ***USA:*** Thrombate III.