Thrombin *(rINN)*

Factor IIa; Thrombine; Thrombinum; Trombin; Trombina.

Тромбин

CAS — 9002-04-4.
ATC — B02BC06; B02BD30.
ATC Vet — QB02BC06; QB02BD30.

Pharmacopoeias. Many pharmacopoeias have monographs, including *US*.

USP 31 (Thrombin). A sterile, freeze-dried powder derived from bovine plasma containing the protein substance prepared from prothrombin through interaction with added thromboplastin in the presence of calcium. It is capable, without the addition of other substances, of causing the clotting of whole blood, plasma, or a solution of fibrinogen. It should be stored at 2° to 8°. Once reconstituted, solutions should be used within a few hours of preparation. The label should state that the prepared solution should not be injected into or otherwise allowed to enter large blood vessels.

A white to greyish, amorphous substance dried from the frozen state.

Thrombin Alfa *(USAN, rINN)*

Human thrombin (recombinant, glycosylated); Thrombine Alfa; Thrombinum Alfa; Trombina Alfa. Human thrombin (recombinant, glycofrom α).

Тромбин Альфа

CAS — 869858-13-9.

Adverse Effects and Precautions

Hypersensitivity reactions, including anaphylaxis, have occurred rarely. Thrombin solutions must not be injected into blood vessels.

Antibody formation. Exposure to thrombin preparations of bovine origin has led to the development of antibodies to bovine thrombin and factor V with cross-reactivity, in some cases, to human factors. The presence of inhibitors to human factors may produce bleeding abnormalities and interfere with clotting measurements. Platelet infusions, fresh frozen plasma, and activated prothrombin complex concentrates have been used in the management of acute haemorrhagic complications, though often with limited success. Treatments that have been tried, in order to reduce the antibody titre, have included corticosteroids, ciclosporin, antineoplastics, intravenous immunoglobulin, and plasmapheresis.[1,2] Despite the availability of preparations containing virus-inactivated human fibrinogen the use of bovine thrombin is reported to be widespread and cases of acquired factor V inhibitor continue to occur.[3]

1. Ortel TL. Clinical and laboratory manifestations of anti-factor V antibodies. *J Lab Clin Med* 1999; **133:** 326–34.
2. Streiff MB, Ness PM. Acquired FV inhibitors: a needless iatrogenic complication of bovine thrombin exposure. *Transfusion* 2002; **42:** 18–26.
3. Kirkeby KM, Aronowitz P. Acquired factor V inhibitor: a common and avoidable complication of topical bovine thrombin application. *Am J Med* 2005; **118:** 805.

Uses and Administration

Thrombin is a protein substance produced *in vivo* from prothrombin that converts soluble fibrinogen into insoluble fibrin thus producing coagulation.

Thrombin of either human or bovine origin is applied topically to control bleeding from capillaries and small venules. It is applied directly to the bleeding surface either as a solution or dry powder. It may also be used with absorbable gelatin sponge during surgical procedures. Thrombin alfa, a recombinant human thrombin, is used similarly.

Thrombin is a component of fibrin glue (p.1069).

General references. Reviews.

1. Lundblad RL, *et al.* A review of the therapeutic uses of thrombin. *Thromb Haemost* 2004; **91:** 851–60.

Pseudoaneurysm. An acute pseudoaneurysm is an arterial rupture, contained by fibromuscular tissue, that communicates with the artery via a narrow neck. Insertion-site femoral pseudoaneurysm can occur as a result of procedures such as cardiac catheterisation and peripheral angiography. It is usually treated with ultrasound-guided compression, but this time-consuming technique causes discomfort for both the patient and the staff carrying out the procedure, and may be of limited success for large pseudoaneurysms and patients receiving anticoagulation. Surgical repair may be required in some patients. As an alternative to pressure or surgery, thrombin has been given by ultrasound-guided percutaneous injection. In reported series,[1-4] complete thrombosis of the pseudoaneurysm sac occurred in more than 90% of patients with one injection of bovine thrombin. Bovine thrombin has also been used when compression has failed,[4,5] and a comparative study[6] in 30 patients found thrombin to be more successful than compression. Human thrombin has also been used successfully.[7] A retrospective review[8] concluded that bovine and human thrombin were equally effective. The successful use of autologous thrombin in a few patients has also been described.[9]

1. La Perna L, *et al.* Ultrasound-guided thrombin injection for the treatment of postcatheterization pseudoaneurysms. *Circulation* 2000; **102:** 2391–5.
2. Mohler ER, *et al.* Therapeutic thrombin injection of pseudoaneurysms: a multicenter experience. *Vasc Med* 2001; **6:** 241–4.
3. Olsen DM, *et al.* A prospective study of ultrasound scan-guided thrombin injection of femoral pseudoaneurysm: a trend toward minimal medication. *J Vasc Surg* 2002; **36:** 779–82.
4. Stone P, *et al.* Iatrogenic pseudoaneurysms: comparison of treatment modalities, including duplex-guided thrombin injection. *W V Med J* 2003; **99:** 230–2.
5. Lönn L, *et al.* Treatment of femoral pseudoaneurysms: percutaneous US-guided thrombin injection versus US-guided compression. *Acta Radiol* 2002; **43:** 396–400.
6. Lönn L, *et al.* Prospective randomized study comparing ultrasound-guided thrombin injection to compression in the treatment of femoral pseudoaneurysms. *J Endovasc Ther* 2004; **11:** 570–6.
7. Maleux G, *et al.* Percutaneous injection of human thrombin to treat iatrogenic femoral pseudoaneurysms: short- and midterm ultrasound follow-up. *Eur Radiol* 2003; **13:** 209–12.
8. Vázquez V, *et al.* Human thrombin for treatment of pseudoaneurysms: comparison of bovine and human thrombin sonogram-guided injection. *Am J Roentg* 2005; **184:** 1665–71.
9. Quarmby JW, *et al.* Autologous thrombin for treatment of pseudoaneurysms. *Lancet* 2002; **359:** 946–7.

Preparations

Ph. Eur.: Fibrin Sealant Kit;
USP 31: Thrombin.

Proprietary Preparations (details are given in Part 3)
Austral.: Thrombostat†; ***Canad.:*** Thrombostat†; ***NZ:*** Thrombostat; ***Pol.:*** Gastrotrombina; ***S.Afr.:*** Tisseel; ***USA:*** Evithrom; Recothrom; Thrombinar; Thrombogen†; Thrombostat.

Multi-ingredient: ***Arg.:*** Beriplast P; Tissucol; Tissucol Duo Quick†; ***Austral.:*** Tisseel Duo; ***Austria:*** Beriplast; TachoComb; TachoSil; Tissucol; Tissucol Duo Quick; ***Belg.:*** Tissucol Duo; ***Braz.:*** Beriplast P; Tissucol†; ***Canad.:*** Tisseel; ***Chile:*** Beriplast P; ***Cz.:*** TachoComb†; TachoSil; Tissucol; ***Denm.:*** TachoSil; Tisseel Duo Quick; ***Fin.:*** TachoSil; Tisseel Duo Quick; ***Fr.:*** Beriplast; Quixil; TachoSil; Tissucol; ***Ger.:*** Beriplast; Quixil; TachoComb†; TachoSil; Tissucol Duo S; Tissucol-Kit; ***Gr.:*** Beriplast P; ***Hong Kong:*** Beriplast P; TachoComb; Tisseel; ***Hung.:*** Beriplast P; TachoComb†; Tissucol-Kit; ***Indon.:*** Beriplast; ***Israel:*** Beriplast; Quixil; Tisseel; ***Ital.:*** Beriplast; Quixil; TachoSil; Tissucol; ***Mex.:*** Beriplast P; Tissucol†; ***Neth.:*** Beriplast P; Quixil; TachoSil; Tissucol; Tissucol Duo; ***Norw.:*** TachoSil; ***Pol.:*** Beriplast; ***Port.:*** Quixil; TachoSil; Tissucol Duo; ***Rus.:*** TachoComb (ТахоКомб); ***Spain:*** Beriplast P Combi; TachoSil; Tissucol Duo; ***Swed.:*** TachoSil; Tisseel Duo Quick; ***Switz.:*** Beriplast P; TachoSil; Tissucol; Tissucol Duo S; ***Thai.:*** Fibrin Glue†; TachoComb†; ***Turk.:*** Beriplast P; Tisseel VH; ***UK:*** TachoSil; Tisseel; ***USA:*** Artiss.

Thrombomodulin Alfa *(rINN)*

ART-123; Thrombomoduline Alfa; Thrombomodulinum Alfa; Trombomodulina alfa. 1–498-Thrombomodulin (human clone TMP26/TMJ1 protein moiety reduced).

Тромбомодулин Альфа

CAS — 120313-91-9.

Profile

Endogenous thrombomodulin is a transmembrane protein found on the surface of endothelial cells, which acts as a thrombin receptor. Thrombomodulin-bound thrombin activates protein C, which then inactivates clotting factors and so limits coagulation.

Thrombomodulin alfa, a recombinant form of thrombomodulin, is under investigation in the prophylaxis of venous thromboembolism and the treatment of disseminated intravascular coagulation.

◊ References.

1. Kearon C, *et al.* Dose-response study of recombinant human soluble thrombomodulin (ART-123) in the prevention of venous thromboembolism after total hip replacement. *J Thromb Haemost* 2005; **3:** 962–8.
2. Saito H, *et al.* Efficacy and safety of recombinant human soluble thrombomodulin (ART-123) in disseminated intravascular coagulation: results of a phase III, randomized, double-blind clinical trial. *J Thromb Haemost* 2007; **5:** 31–41.

Thromboplastin

Cytozyme; Thrombokinase; Tromboplastina; Tromboplastyna.

Profile

Tissue thromboplastin (tissue factor; factor III) is a membrane glycoprotein that is released from damaged tissue and initiates coagulation. The term thromboplastin may also be applied to other related substances with similar activity. Commercial preparations may contain tissue extracts comprising a variety of such substances.

Preparations of thromboplastin have been used as haemostatics.

A preparation of thromboplastin derived from rabbit brain is used in the determination of the prothrombin time for the control of anticoagulant therapy (for further details see Uses and Administration of Warfarin Sodium, p.1432).

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Clauden.

Multi-ingredient: ***Braz.:*** Claudemor; ***Port.:*** Claudemor†; ***Venez.:*** Claudemor†.

Thrombopoietin

Trombopoyetina.

Profile

Thrombopoietin is a naturally occurring colony-stimulating factor that regulates thrombopoiesis (see Haematopoiesis, p.1042). Recombinant thrombopoietin, and a form of recombinant thrombopoietin conjugated with polyethylene glycol (pegacaristim, PEG-megakaryocyte growth and development factor, PEG-rHuMGDF), are under investigation. They have been studied in the management of thrombocytopenia (p.1051) in patients receiving myelosuppressive or myeloablative chemotherapy, and in patients with myelodysplastic syndrome or HIV-associated thrombocytopenia. There is also some interest in the use of recombinant forms of thrombopoietin in stem cell mobilisation regimens and to increase platelet counts in healthy apheresis donors. However, some results have been disappointing and there are reports of neutralising antibody development.

General references. Studies and reviews.

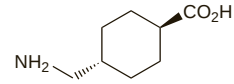
1. Vadhan-Raj S, *et al.* Safety and efficacy of transfusions of autologous cryopreserved platelets derived from recombinant human thrombopoietin to support chemotherapy-associated severe thrombocytopenia: a randomised cross-over study. *Lancet* 2002; **359:** 2145–52.
2. Nomura S, *et al.* Effects of pegylated recombinant human megakaryocyte growth and development factor in patients with idiopathic thrombocytopenic purpura. *Blood* 2002; **100:** 728–30.
3. Schuster MW, *et al.* The effects of pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) on platelet recovery in breast cancer patients undergoing autologous bone marrow transplantation. *Exp Hematol* 2002; **30:** 1044–50.
4. Kuter DJ, Begley CG. Recombinant human thrombopoietin: basic biology and evaluation of clinical studies. *Blood* 2002; **100:** 3457–69.
5. Linker C, *et al.* Recombinant human thrombopoietin augments mobilization of peripheral blood progenitor cells for autologous transplantation. *Biol Blood Marrow Transplant* 2003; **9:** 405–13.
6. Vadhan-Raj S, *et al.* Importance of predosing of recombinant human thrombopoietin to reduce chemotherapy-induced early thrombocytopenia. *J Clin Oncol* 2003; **21:** 3158–67.
7. Geissler K, *et al.* Prior and concurrent administration of recombinant human megakaryocyte growth and development factor in patients receiving consolidation chemotherapy for de novo acute myeloid leukemia—a randomized, placebo-controlled, double-blind safety and efficacy study. *Ann Hematol* 2003; **82:** 677–83.

Tranexamic Acid *(BAN, USAN, rINN)*

Acide tranexamique; Ácido tranexámico; Acidum tranexamicum; AMCA; *trans*-AMCHA; CL-65336; Kyselina tranexamová; Traneksaamihappo; Traneksamik Asit; Traneksamo rūgštis; Tranexámsav; Tranexamsyra. *trans*-4-(Aminomethyl)cyclohexanecarboxylic acid.

Транексамовая Кислота

$C_8H_{15}NO_2$ = 157.2.
CAS — 1197-18-8.
ATC — B02AA02.
ATC Vet — QB02AA02.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Tranexamic Acid). A white or almost white, crystalline powder. Freely soluble in water and in glacial acetic acid; practically insoluble in alcohol and in acetone. A 5% solution in water has a pH of 7.0 to 8.0.

Incompatibility. Solutions of tranexamic acid are incompatible with benzylpenicillin.

Adverse Effects

Tranexamic acid appears to be well tolerated. It can produce dose-related gastrointestinal disturbances. Hypotension has occurred, particularly after rapid intravenous dosage. Thrombotic complications have been reported in patients receiving tranexamic acid, but these are usually a consequence of its inappropriate use (see Precautions, below). There have been a few instances of transient disturbance of colour vision associated with use of tranexamic acid; in such cases the drug should be stopped. Hypersensitivity skin reactions have also been reported.

Effects on the eyes. Tranexamic acid has been associated with retinopathy[1] and visual impairment.[2] A haemodialysis patient developed almost total loss of vision within 2 weeks of starting daily tranexamic acid injections after emergency surgery for a bleeding peptic ulcer. Vision was largely restored within a few days of stopping tranexamic acid,[2] although some impairment persisted in conditions of poor light. The patient had experienced visual impairment previously when given tranexamic acid. The authors noted that doses of tranexamic acid should be reduced in patients with renal impairment undergoing dialysis.

A patient undergoing regular peritoneal dialysis for Epstein's syndrome developed ligneous conjunctivitis, gingival hyperpla-